Organic Reactions

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the investigator will be able

▼

to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

CONTENTS

CHAPTER 1

CYCLOBUTANE DERIVATIVES FROM THERMAL CYCLOADDITION REACTIONS*

JOHN D. ROBERTS AND CLAY M. SHARTS†

California Institute of Technology

CONTENTS

INTRODUCTION

Preparation of substituted cyclobutanes and cyclobutenes by cyclo-addition reactions of alkene to alkene and alkene to alkyne has become an important synthetic reaction and, in fact, where applicable, is now the method of choice for synthesis of four-membered carbon ring compounds. Such cycloadditions may be achieved thermally under autogenous pressure in the presence of free-radical inhibitors or photochemically by irradiation with visible or ultraviolet light. This chapter does not include photochemical cycloadditions or the thermal dimerizations of ketenes since these have been well reviewed elsewhere.[1-3]

Historically, the establishment of cyclobutane structures for cyclo-addition products provides an enlightening example of the waxing and waning of fashions in the interpretation of organic reactions. Some of the interesting and important landmarks will be briefly noted here.* First, the early work of Liebermann[4] (1889) on the truxillic acids provided a strong measure of confidence for later workers in assigning cyclobutane structures to a variety of cycloadducts, and, when Kraemer[5] discovered dicyclopentadiene (1896), he suggested that it was a cyclobutane derivative. This was followed by proposals of cyclobutane structures for dimers from 1,5-cyclooctadiene (Willstätter,[6] 1905), substituted ketenes (Staudinger,[7] 1906–1912), unsaturated acids (Doebner,[8] 1907), and allenes (Lebedev,[9] 1911–1913). Publication by Staudinger[10] of *Die Ketene* in 1912 appeared to complete the conditioning of chemical thought, and postulation of formation of cyclobutanes by cycloaddition reactions was both fashionable and respectable over the next two decades.

[1] Mustafa, *Chem. Revs.*, **51**, 1 (1952).

[2] Hanford and Sauer, *Org. Reactions*, **3**, 108–140 (1946).

[3] Some additional material is given in reviews by Vogel, *Fortschr. chem. Forsch.*, **3**, 430 (1955); R. A. Raphael, in Rodd, *Chemistry of Carbon Compounds*, Vol. IIA, Chap. 3, Elsevier, 1953.

* This paragraph and the following paragraph are based on a survey kindly provided by Dr. Edwin R. Buchman.

[4] Liebermann, *Ber.*, **22**, 2240 (1889); **23**, 2516 (1890).

[5] Kraemer and Spilker, *Ber.*, **29**, 552 (1896); Wieland, *Ber.*, **39**, 1492 (1906).

[6] Willstätter and Veraguth, *Ber.*, **38**, 1975 (1905). Actually, these workers only noted that the formation of dimeric 1,5-cyclooctadiene had a parallel in the dimerization of cyclopentadiene, and they referred to the paper by Kraemer and Spilker,[5] where a cyclobutane structure is suggested for dicyclopentadiene. The cyclobutane structure for dimeric 1,5-cyclooctadiene was not definitely proposed until much later by Ziegler, Sauer, Bruns, Froitzheim-Kühlhorn, and Schneider, *Ann.*, **589**, 122 (1954).

[7] Staudinger and Klever, *Ber.*, **39**, 968 (1906); **40**, 1140 (1907); Staudinger, *Ber.*, **40**, 1145 (1907), and later papers.

[8] Doebner, *Ber.*, **40**, 146 (1907).

[9] Lebedev, *J. Russ. Phys. Chem. Soc.*, **45**, 1357 (1913) [*C.A.*, **9**, 799 (1915)].

[10] Staudinger, *Die Ketene*, Enke, Stuttgart, 1912.

The skies darkened briefly in 1928 when Diels and Alder[11] demonstrated the generality of their reaction and suggested that dicyclopentadiene resulted from 1,4 and not 1,2 addition. However, Bergel[12] in 1928 reaffirmed faith in the cyclobutane structure, and comparative peace
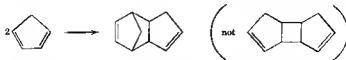
reigned until 1931 when Alder and Stein[13] proved beyond reasonable doubt that dicyclopentadiene actually had the bridged-ring structure. With this development, cyclobutane structures for cycloadducts rapidly became unfashionable and fell into general disfavor. The tide was finally stemmed in 1934 when Cupery and Carothers[14] oxidized the dimer of divinylacetylene to cyclobutane-1,2-dicarboxylic acid—the first time a cyclobutane derivative of known structure was isolated as a degradation product of a cycloadduct. None the less, the tenor of thought in the late thirties was such that when Simonsen[15] showed that Staudinger's diphenyl-ketene-cyclopentadiene adduct contained a four-membered ring, this result was "not anticipated." The pessimism which then prevailed is well illustrated by Bergmann's review article of 1939[16] in which many postulated cyclobutane structures (some correct, some incorrect) were flatly rejected. The era of doubt drew to a close late in the forties when new experimental results led to general recognition of the usefulness of thermal cycloaddition reactions as a synthetic route to cyclobutane derivatives.

The breakthrough was greatly facilitated by the discovery of du Pont research groups[17,18] that octafluorocyclobutane can be formed readily by thermal dimerization of tetrafluoroethylene. This development inspired several extensive investigations of cycloadditions involving fluoroalkenes. A typical reaction is the addition of tetrafluoroethylene to 1,3-butadiene at 125° to afford 3-vinyl-1,1,2,2-tetrafluorocyclobutane in 90% yield.[19] This cycloaddition illustrates two important points. First, fluorinated

[11] Diels and Alder, *Ann.*, **460**, 99 (1928)
[12] Bergel and Widmann, *Ann.*, **467**, 79 (1928)
[13] Alder and Stein, *Ann.*, **485**, 223 (1931), **501**, 247 (1933)
[14] Cupery and Carothers, *J Am Chem Soc*, **56**, 1167 (1934).
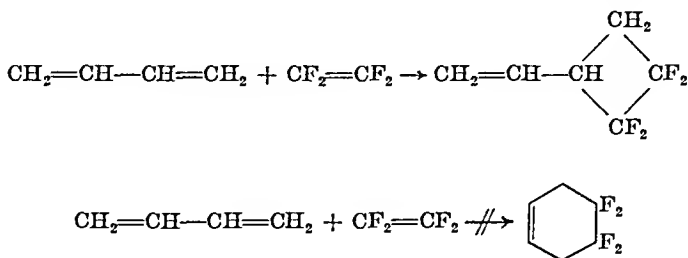[15] Lewis, Ramage, Simonsen, and Wainwright, *J Chem Soc* 1937, 1831.
[16] Bergmann, *Trans Faraday Soc*, **35**, 1025 (1939)
[17] Benning, Downing, and Park, U.S. pat 2,384,821 [C.A., 40, 3460 (1946)].
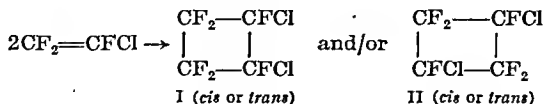[18] Lewis and Naylor, *J Am Chem Soc*, **69**, 1968 (1947)
[19] Coffman, Barrick, Cramer, and Raasch, *J Am Chem Soc*, **71**, 490 (1949)

alkenes may add to non-fluorinated unsaturated compounds much more readily than they dimerize. Second, when fluorinated alkenes are given

$$CH_2{=}CH{-}CH{=}CH_2 + CF_2{=}CF_2 \rightarrow CH_2{=}CH{-}CH\overset{\displaystyle CH_2}{\underset{\displaystyle CF_2}{\diagup\diagdown}}CF_2$$

$$CH_2{=}CH{-}CH{=}CH_2 + CF_2{=}CF_2 \not\rightarrow \hexagon F_2$$

a choice between four- and six-membered ring formation, as is possible with a conjugated diene, the formation of the four-membered ring is favored. It seems significant that ethylene[20] and tetracyanoethylene[21] apparently give only the normal Diels-Alder, six-membered ring products with butadiene.

The experimental conditions for the addition of tetrafluoroethylene to butadiene are very similar to those commonly used for Diels-Alder reactions involving volatile addends, and a further similarity is provided by the aforementioned fact that two dissimilar compounds, tetrafluoroethylene and butadiene, are found to react with each other much more readily than they react with themselves. Like Diels-Alder reactions,[22] the cycloadditions leading to four-membered rings may present orientational and stereochemical problems. For example, dimerization of trifluorochloroethylene can give two structural isomers, the "head-to-head" (I) and "head-to-tail" (II) adducts, and each of these may be the *cis* or the

$$2CF_2{=}CFCl \rightarrow \underset{\text{I }(cis\ or\ trans)}{\begin{array}{c} CF_2{-}CFCl \\ | \qquad | \\ CF_2{-}CFCl \end{array}} \quad \text{and/or} \quad \underset{\text{II }(cis\ or\ trans)}{\begin{array}{c} CF_2{-}CFCl \\ | \qquad | \\ CFCl{-}CF_2 \end{array}}$$

trans isomer. It is of considerable practical and theoretical significance that the principal product in this[23] and other cases is the result of head-to-head addition (I) with the chlorine atoms predominantly *cis* to one another. This mode of addition is not at all peculiar to fluoroalkenes. Allene dimerizes to give predominantly 1,2-dimethylenecyclobutane[9,24]

[20] Joshel and Butz, *J. Am. Chem. Soc.*, **63**, 3350 (1941).
[21] Middleton, Heckert, Little, and Krespan, *J. Am. Chem. Soc.*, **80**, 2783 (1958).
[22] Holmes, *Org. Reactions*, **4**, 62–64 (1948).
[23] Lacher, Tompkin, and Park, *J. Am. Chem. Soc.*, **74**, 1693 (1952).
[24] Williams and Sharkey, *J. Am. Chem. Soc.*, **81**, 4269 (1959).

(head-to-head), and acrylonitrile affords *cis*- and *trans*-1,2-dicyanocyclo-butane.[25] As will be shown, these facts are strong evidence against ionic
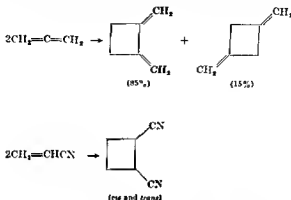
mechanisms for this type of cycloaddition (except possibly ketene dimerizations); in addition, they may well provide new understanding of factors governing cycloadditions in general, including the Diels-Alder reaction. None the less, some success has been achieved in utilizing the beneficial effect of *gem*-fluorine atoms on formation of four-membered rings and then removing the fluorine by hydrolysis to yield carbonyl groups. In this way, practical laboratory syntheses have been developed of substituted cyclobutenones (III, IV),[26-28] cyclobutenediones (V to VII),[29-31] and tropolone (VIII).[31] as illustrated in the following equations.

[25] Coyner and Hillman, *J Am Chem Soc*, **71**, 324 (1949)
[26] Roberts, Kline, and Simmons, *J Am Chem Soc*, **75**, 4765 (1953).
[27] Silversmith, Kitahara, Caserio, and Roberts, *J Am Chem Soc*, **80**, 5840 (1958)
[28] Roberts, *Record Chem Progr*, **17**, 95 (1956)
[29] Smutny and Roberts, *J Am Chem Soc*, **77**, 3420 (1955).
[30] Blomquist and La Lancette, Abstr of American Chemical Society Meeting, Boston, Mass, April, 1959, p 54 O
[31] Cohen, Lacher, and Park, *J Am Chem Soc*, **81**, 3480 (1959)
[32] Drysdale, Gilbert, Sinclair and Sharkey, *J Am Chem Soc*, **80**, 245, 3672 (1958)

$$C_6H_5C\equiv CH + CCl_2=CF_2 \rightarrow C_6H_5C \begin{array}{c} CH \\ \diagdown \\ CCl_2 \end{array} CF_2 \xrightarrow{H_2SO_4} C_6H_5C \begin{array}{c} CH \\ \diagdown \\ CCl_2 \end{array} C=O$$
<div align="center">III</div>

$$C_6H_5CH=CH_2 + CCl_2=CF_2 \rightarrow C_6H_5CH \begin{array}{c} CH_2 \\ \diagdown \\ CCl_2 \end{array} CF_2 \xrightarrow{t\text{-}C_4H_9OK}$$

$$C_6H_5C \begin{array}{c} CH_2 \\ \diagdown \\ C \\ | \\ OC_4H_9\text{-}t \end{array} CF_2 \xrightarrow{H_2SO_4} C_6H_5C \begin{array}{c} CH_2 \\ \diagdown \\ C \\ | \\ OH \end{array} C=O$$
<div align="center">IV</div>

$$C_6H_5C\equiv CH + CFCl=CF_2 \rightarrow C_6H_5C \begin{array}{c} CH \\ \diagdown \\ CCIF \end{array} CF_2 \xrightarrow{H_2SO_4} C_6H_5C \begin{array}{c} CH \\ \diagdown \\ C \\ || \\ O \end{array} C=O$$
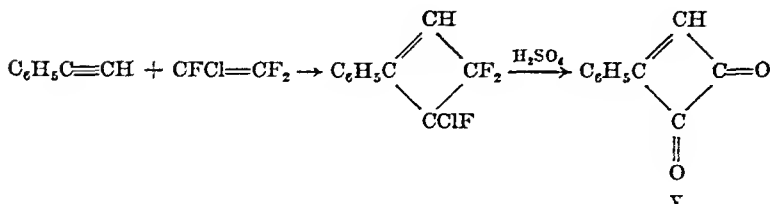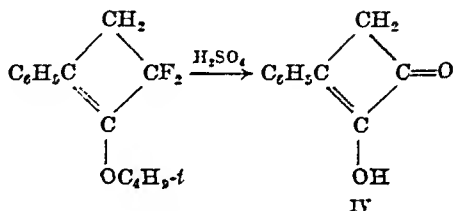<div align="center">V</div>

$$2CFCl=CF_2 \rightarrow \begin{array}{c} CFCl—CF_2 \\ | \quad\quad | \\ CFCl—CF_2 \end{array} \xrightarrow{Zn} \begin{array}{c} CF—CF_2 \\ || \quad\quad | \\ CF—CF_2 \end{array} \xrightarrow{2C_6H_5Li}$$

The cycloadduct IX from ketene and cyclopentadiene, even though formed in rather poor yield, has been used as an intermediate for the synthesis of a bicyclo[3.3.0]octadiene as part of a projected route to pentalene[33] and has also been converted to cycloheptatriene.[34]
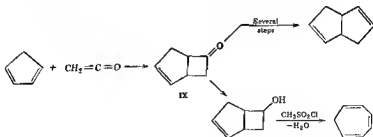
The very reasonable yields of cyclobutane derivatives recently demonstrated for the addition of allene to various substituted alkenes[35] have

[33] Roberts and Gorham, *J Am Chem. Soc.*, **74**, 2278 (1952).

[34] Dryden, Jr , *J Am Chem Soc*, **76**, 2841 (1954).

[35] Cripps Williams and Sharkey *J Am Chem Soc*, **80**, 751 (1958)

substantially broadened the synthetic usefulness of the cycloaddition reaction for the preparation of non-fluorinated, four-membered-ring compounds. The adduct X from allene and acrylonitrile has already proved useful in syntheses for 1,3-dimethylenecyclobutane,[36, 37] 3-methylenecyclobutanone,[38] and 1,3-cyclobutanedione.[39]
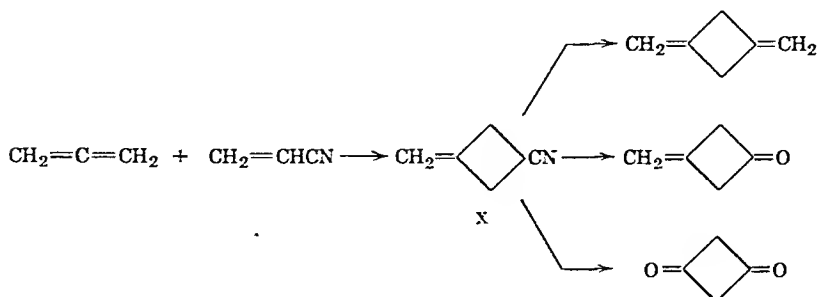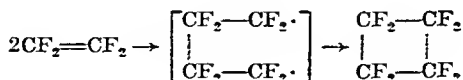

$$CH_2{=}C{=}CH_2 \ + \ CH_2{=}CHCN \longrightarrow CH_2{=}\langle\ \rangle CN \longrightarrow$$

X

REACTION MECHANISM

It has been suggested that formation of octafluorocyclobutane from tetrafluoroethylene during the pyrolysis of polytetrafluoroethylene (Teflon) involves a diradical intermediate.[18] A similar explanation was

$$2CF_2{=}CF_2 \rightarrow \begin{bmatrix} CF_2{-}CF_2{\cdot} \\ | \\ CF_2{-}CF_2{\cdot} \end{bmatrix} \rightarrow \begin{matrix} CF_2{-}CF_2 \\ | \quad | \\ CF_2{-}CF_2 \end{matrix}$$

offered to account for the head-to-head dimerization of acrylonitrile.[25] Formation of the diradical XI was expected to be substantially more

$$2CH_2{=}CHCN \rightarrow \begin{bmatrix} CH_2{-}CH{-}CN \\ | \quad \cdot \\ CH_2{-}CH{-}CN \end{bmatrix} \rightarrow \begin{matrix} CH_2{-}CHCN \\ | \quad | \\ CH_2{-}CHCN \end{matrix}$$

XI
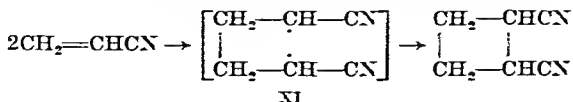
favorable than formation of the diradical XII, which would also lead to head-to-head cycloaddition, or XIII, which would give the head-to-tail product because of stabilization resulting through interaction of the unpaired electrons with the adjacent unsaturated cyano groups as may

[36] Caserio, Jr., Parker, Piccolini, and Roberts, J. Am. Chem. Soc., 80, 5507 (1958).
[37] Cripps, Williams, and Sharkey, J. Am. Chem. Soc., 81, 2723 (1959).
[38] Caserio, Jr. and Roberts, J. Am. Chem. Soc., 80, 5837 (1958).
[39] E. Renk and J. D. Roberts, unpublished research.

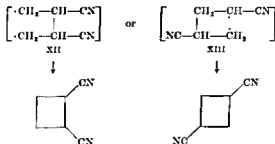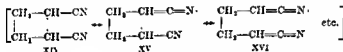$$\begin{bmatrix} \cdot CH_2-CH-CN \\ | \\ \cdot CH_2-CH-CN \end{bmatrix} \quad \text{or} \quad \begin{bmatrix} \cdot CH_2-CH-CN \\ | \\ NC-CH-CH_2 \cdot \end{bmatrix}$$

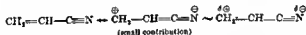$$XII \qquad\qquad\qquad XIII$$

be symbolized by the resonance forms XIV to XVI, etc. Such stabilization would be possible for only one of the unpaired electrons of diradical XIII and would be impossible for XII.

$$\begin{bmatrix} CH_2-CH-CN \\ | \\ CH_2-CH-CN \end{bmatrix} \leftrightarrow \begin{bmatrix} CH_2-CH=C=N\cdot \\ | \\ CH_2-CH-CN \end{bmatrix} \leftrightarrow \begin{bmatrix} CH_2-CH=C=N\cdot \\ | \\ CH_2-CH=C=N\cdot \end{bmatrix} \quad etc.$$

$$XIV \qquad\qquad XV \qquad\qquad XVI$$

The head-to-head orientation produced with acrylonitrile appears to exclude an ionic mechanism since the electrical polarization of the double

$$CH_2=CH-C≡N \leftrightarrow \overset{\oplus}{CH_2}-CH=C=\overset{\ominus}{N} \sim \overset{\ominus}{CH_2}-CH-C≡\overset{\oplus}{N}$$
$$\text{(small contribution)}$$

bond by the cyano group would be expected to lead exclusively to head-to-tail addition. Furthermore, an ionic intermediate (XVII) analogous to the diradical XI would have a cationic center immediately adjacent to a cyano group, and there seems to be no reason to suppose that this unfavorable juxtaposition of electron-withdrawing groups would necessarily be more than counterbalanced by the concomitant establishment of an anionic center adjacent to the other cyano group. An additional argument against ionic mechanisms is that these cycloadditions proceed well in non-polar solvents and with fluoroalkenes even in the gas phase.[23]

$$\begin{bmatrix} CH_2-CH-C≡N \\ | \overset{\oplus}{} \\ CH_2-CH-C≡N \end{bmatrix}$$

$$XVII$$
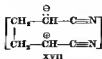
The reasonable alternative to the stepwise diradical mechanism is a more or less concerted breaking of the multiple bonds of the addends and formation of the new bonds of the adduct. If the 1,4 bond has only a

very slight single-bond character in the transition state when formation of the 2,3 bond is nearly complete, we have what might be termed a "virtual" diradical mechanism. The distinction between this formulation and the "bona fide" diradical process proposed by Coyner and Hillman[25] is that the electrons are regarded as remaining paired at all times in the concerted mechanism and sufficient bonding exists between C-1 and C-4 to prevent free rotation about the 1,2 and 3,4 bonds. The free-valence index at the 1 and 4 positions in the transition state might well be sufficiently great that predictions of orientation can be made for unsymmetrical alkenes on the same successful basis as is possible with the diradical mechanism (see later).
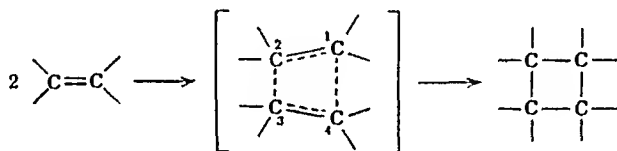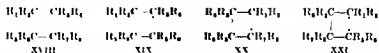

The possible role of charge-transfer complexes of the type postulated for the Diels-Alder reaction[40] as intermediates in formation of cyclobutane derivatives by cycloaddition reactions is by no means clear. Tetrafluoroethylene and similar substances are hardly expected to function well as both donor and acceptor moieties in forming charge-transfer complexes. None the less, such substances may dimerize smoothly to cyclobutane derivatives. On this basis, it seems best to conclude that formation of charge-transfer intermediates should not be regarded as a necessary condition for cycloaddition. However, as mentioned earlier, tetrafluoroethylene and butadiene react with each other more easily than either reacts with itself. This fact indicates that mutual polarization (or something akin to charge transfer) aids in stabilizing the cycloaddition transition state whatever the detailed features of the reaction mechanism may be.

Second-order kinetics have been established for the gas-phase dimerization of some fluoroalkenes,[23] and activation parameters are available.[23] The results provide no help for distinguishing between the stepwise and concerted mechanisms.

The diradical mechanism for cycloaddition possesses the virtue of being extremely useful for predicting the course of cycloaddition with unsymmetrical ethylenes. For the general case of addition of $R_1R_2C{=}CR_3R_4$ to $R_5R_6C{=}CR_7R_8$, one can write four possible diradical intermediates

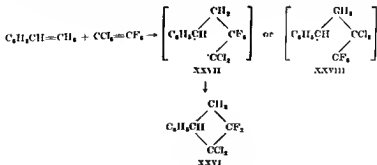[40] Kloetzel, *Org. Reactions*, **4**, 1–59 (1948).

XVIII to XXI   The problem of predicting the direction of addition then reduces to the problem of predicting which of the diradicals would be the most stable on electronic or steric grounds or both   Usually it appears

$$R_2H_2C\cdot\quad\cdot CH_2R_1 \qquad R_2H_2C\cdot\quad\cdot CHR_6 \qquad R_6R_2C\cdot\quad\cdot CH_2R_1 \qquad R_2H_2C\cdot\quad\cdot CHR_6$$

$$R_4R_3C\cdot\quad\cdot CH_2R_5 \qquad R_4R_3C\cdot\quad\cdot CR_3R_5 \qquad R_6R_3C\cdot\quad\cdot CR_3R_5 \qquad R_4H_2C\cdot\quad\cdot CR_3R_5$$

$$\text{XVIII} \qquad\qquad \text{XIX} \qquad\qquad \text{XX} \qquad\qquad \text{XXI}$$

as though electronic considerations are the more important.   As an example consider the addition of ketene to cyclopentadiene.   The four possible diradicals are XXII to XXV   Of these, XXIII is expected to be most stable because both odd electrons could be stabilized by interaction with an unsaturated group.   The product obtained, IX, is that expected from a ring closure involving XXIII.

$$\text{XXII} \qquad\qquad \text{XXIII} \qquad\qquad \text{XXIV} \qquad\qquad \text{XXV}$$
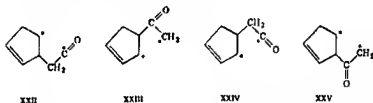
Similar arguments applied to the addition of dichlorodifluoroethylene to styrene suggest that the adduct should be XXVI, which is expected to arise from the diradical XXVII.   The formulation XXVII is considered to be more favorable than XXVIII on the basis that a difluoromethyl radical should be less stable than a dichloromethyl radical.[41]   The observed cycloaddition product is XXVI,[27] in accord with predictions.

$$C_6H_5CH=CH_2 + CCl_2=CF_2 \rightarrow \left[\begin{array}{c} CH_2 \\ C_6H_5CH \quad CF_2 \\ \cdot\quad\quad\cdot \\ CCl_2 \end{array} \right] \text{ or } \left[\begin{array}{c} CH_2 \\ C_6H_5CH \quad CCl_2 \\ \cdot\quad\quad\cdot \\ CF_2 \end{array} \right]$$

$$\text{XXVII} \qquad\qquad\qquad \text{XXVIII}$$

$$\downarrow$$

$$\begin{array}{c} CH_2 \\ C_6H_5CH \quad CF_2 \\ CCl_2 \end{array}$$

$$\text{XXVI}$$

41 Walling, *Free Radicals in Solution*, p 253, John Wiley & Sons, New York, 1957

This approach has wide utility and seems to fail badly only for ketene dimerizations, which give the head-to-tail products (perhaps by an ionic mechanism; see later discussion). Tentative structures for some cyclo-addition products are assigned in the tables at the end of the chapter on the basis of the diradical mechanism.

Whether or not bona fide diradicals with unpaired electrons are actually the reaction intermediates is very difficult to determine. The same problem has arisen before in connection with the mechanisms of the thermal polymerization of alkenes and the Diels-Alder addition.[42] It is clear that the absence of accelerating effects produced by the usual free-radical initiators or of retarding influences by free-radical inhibitors is no proof against the diradical mechanism, since we are dealing with a reaction for which no obvious accelerating function can be seen for initiators and which need not be retarded by inhibitors because it is not a chain process. It may be that no single interpretation can be put in words which will satisfy everyone; at least, before final attempts are made to rationalize these cycloadditions, some additional experimental evidence and new ideas will be required.

A possible, but by no means compelling, argument in favor of the diradical mechanism follows. Butadiene and tetrafluoroethylene appear to give exclusively the four-membered-ring adduct,[19] while cyclopenta-diene gives a mixture of four- and six-membered-ring products.[32] If tetrafluoroethylene (unlike dienophiles such as maleic anhydride[42]) were able to add to butadiene molecules in the more stable *quasi-trans* con-figuration to give diradicals, the resonance stabilization of the odd electrons in the butadiene half of any given diradical would tend to confer double-bond character on the 1,2 and 2,3 bonds so as to hold the diradical in the extended structure. This would greatly favor formation of a four-membered ring, since a six-membered ring could only be formed if (1) the allyl-type radical were to lose momentarily its resonance stabilization


(quasi-trans)

----
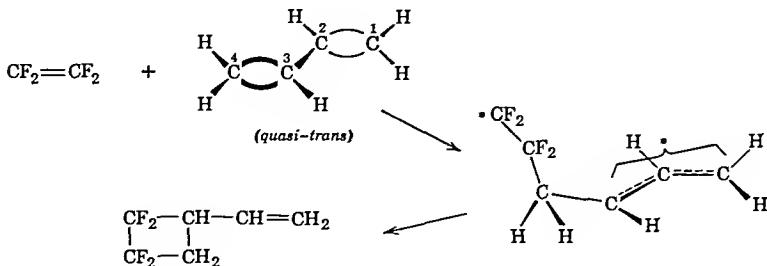
[42] See the excellent discussion by Walling, on pp. 180–189 of ref. 41, and also Woodward and Katz, *Tetrahedron*, 5, 70 (1959).

through a twist about the 2,3 C—C bond, or (2) a six-membered ring containing a *trans* double bond were formed.

With cyclopentadiene, the double bonds can have only the *quasi-cis* relationship to one another; thus the diradical would necessarily possess a configuration which could afford *both* four- and six-membered-ring products, as is observed.[22]
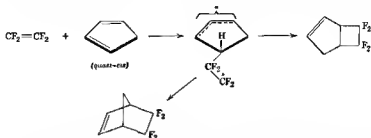
It needs to be determined whether or not one alkene adds to another cleanly in the *cis* manner; a nearly ideal case for the purpose would be afforded by the addition of *cis*(or *trans*-)1,2-dideuteroethylene to tetra-fluoroethylene. The involvement of a bona fide diradical (XXIX) might
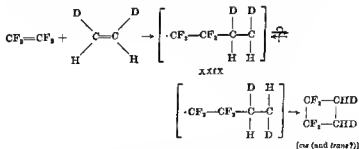
well lead to non-stereospecific addition as the result of rotation about the bond connecting the CHD groups before ring closure.[42]

A number of other questions remain to be answered satisfactorily. Why are *gem*-fluoro compounds, allenes, and ketenes so peculiarly effective in forming four-membered rings even when six-membered rings can be formed, as for example with conjugated dienes? Why do the *double* and
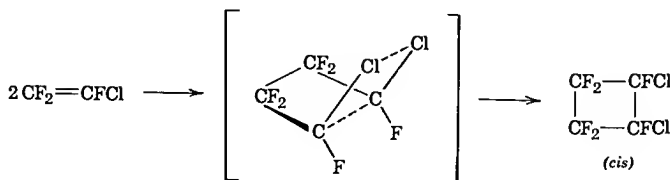
42 Similar considerations have been applied (a) to the mechanistic problem posed by the addition of CH₂ to ethylene. Skell and Garner, *J Am Chem Soc* , 78, 5430 (1956). Skell and Woodworth, *ibid* , 78, 4496 (1956), and (b) to the thermal isomerization of cyclopropane to propene. Rabinovitch, Schlag, and Wiberg, *J Chem. Phys.* 28, 504 (1958)

triple bonds in vinylacetylene react at about the same rate with tetra-fluoroethylene?[19] Are there rules like the Alder rules governing the stereo-chemistry in cycloadditions leading to four-membered rings? Only tentative or partial answers to these questions can now be given.

The effectiveness of *gem*-fluorine atoms in promoting four-membered ring formation may be the result of non-bonding interelectronic repulsions between the fluorine atoms which could tend to increase the $F—C—F$ angle and hence diminish the angle between the other two valences of the carbon atom to which they are attached. Relief of the $F—F$ repulsions would be thus expected to be substantially greater in formation of four-membered rings than of a six-membered ring. This rationalization is, of course, no help in accounting for the behavior of allenes and ketenes.

One thing is clear. Measurements of the activation energies for the forward and reverse processes have shown that the enthalpy of formation of octafluorocyclobutane from two molecules of tetrafluoroethylene is -50 kcal.[44] This value is very much greater than the -25 kcal estimated[44] for formation of cyclobutane from two molecules of ethylene, and it reflects a weak double bond in tetrafluoroethylene and/or a favorable disposition of the fluorine atoms and strong single bonds in octafluoro-cyclobutane.

Few quantitative data about the stereochemistry of additions to form cyclobutanes are available. With acrylonitrile, both *cis*- and *trans*-1,2-dicyanocyclobutane were reported.[25] With 1,3-butadiene, only *trans*-1,2-divinylcyclobutane was isolated along with vinylcyclohexene.[45] However, it is now clear that the *cis* compound is unstable under the reaction conditions and isomerizes to *cis*-*cis*-1,5-cycloöctadiene.[46] Consequently it seems probable that both isomers are actually formed. The dimerization of trifluorochloroethylene gives a 5:1 ratio of head-to-head addition products with preference for the *cis* isomer.[23]* The predominance of *cis*


$$2\,CF_2{=}CFCl \longrightarrow \left[\begin{array}{c} CF_2 \quad Cl \quad Cl \\ CF_2 \qquad C \\ C \qquad F \\ F \end{array} \right] \longrightarrow \begin{array}{c} CF_2{-}CFCl \\ | \qquad | \\ CF_2{-}CFCl \\ (cis) \end{array}$$

[44] Atkinson and Trenwith, *J. Chem. Phys.*, **20**, 754 (1952); *J. Chem. Soc.*, 1953, 2082.

[45] Reed, *J. Chem. Soc.*, 1951, 685.

[46] Vogel, *Angew. Chem.*, **71**, 386 (1959); Vogel and co-workers, *Ann.*, **615**, 1, 29 (1959).

* It is erroneously reported[23] that the symmetry numbers of the products should lead to predominance of *cis* over *trans* addition in the ratio of 2:1. This would be correct only if one optical antipode of the *trans*-dichloro compound were formed. The actual expected statistical ratio is 1:1.

addition here may be due to Cl—Cl dispersion forces operating in the transition state for ring closure[47] (regardless of whether by a concerted or stepwise mechanism) which tend to hold the chlorine atoms *cis* to one another   Similar considerations apply to the apparent formation of the *cis* head-to-head adduct XXX from α-(methylthio)-acrylonitrile [48]
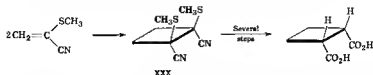
It is clear that some four-membered-ring cycloadditions may be subject to thermodynamic rather than kinetic control   With perfluoropropene, head-to-head addition with apparently a small preference for the *cis* product is observed at 250° while, at 450°, the head-to-tail adduct is formed in the larger amount and the *trans*-1,2 product is greatly favored over the *cis* [49]   Reversible dissociation of the cycloadduct was demonstrated at 390°

A special cycloaddition reaction of considerable interest involves formation of biphenylene by presumed dimerization of benzyne. Biphenylene has been isolated in small to good yields from reactions in
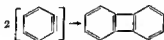
which benzyne was generated by heating [C_6H_4Hg]$_4$ with copper[50] or silver[51] powder, the decomposition of o-fluorophenyllithium,[52] and the reaction of magnesium with o-bromoiodobenzene.[53] It remains to be established whether or not the C—C bonds formed in these reactions are formed essentially simultaneously or in a stepwise manner through o,o'-biphenyl derivatives [51,52]

A few interesting cycloadditions require ionic catalysts   Thus hexachlorocyclopentadiene with trichloroethylene and dichlorobromomethane

[47] Roberts, *J Am Chem Soc*, **72**, 3300 (1950)
[48] Gundermann and Huchting, *Ber*, **92**, 415 (1959)   See also Gundermann and Thomas, *Ber*, **89**, 1263 (1956)
[49] Hauptschein, Fainberg, and Braid, *J Am Chem Soc*, **80**, 842 (1958).
[50] D A Semenow and J D Roberts, unpublished research
[51] Wittig and Bickelhaupt, *Ber*, **91**, 833 (1958)
[52] Wittig and Pohmer, *Ber*, **89**, 1334 (1956)
[53] Heaney, Mann, and Millar, *J Chem Soc*, **1957**, 3930.

and aluminum chloride affords XXXI and XXXII, respectively.[54] Hexachlorocyclopentadiene itself is apparently converted with aluminum chloride to a dimer ($C_{10}Cl_{12}$) with a caged structure possessing three
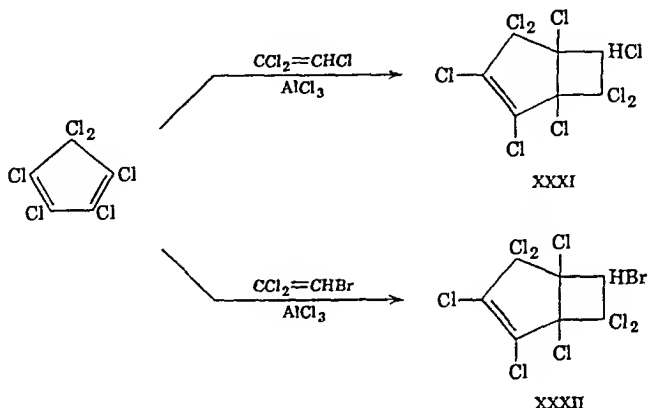
cyclobutane rings.[55] The mechanisms of these processes are unknown, although they may be related to the cyclization reactions discussed below.
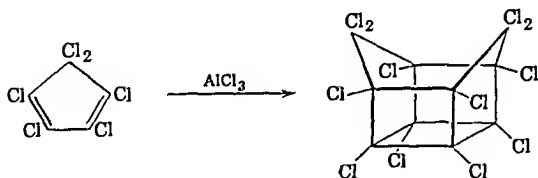
There are a few reactions, which might be classified as cycloadditions, in which cyclobutane derivatives are formed during additions to multiple bonds. The formation of XXXIII in the addition of chlorine (from
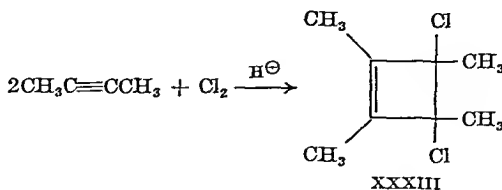
[54] Roedig and Hörnig, *Ann.*, 598, 208 (1956).
[55] Newcomer and McBee, *J. Am. Chem. Soc.*, 71, 952 (1949).

sulfuryl chloride[56] or chlorine in the presence of acid[57] to dimethyl-
acetylene is one example, and the formation of a bridged dibromide in the
addition of bromine to cyclooctatetrene is another.[58]

It is possible that the acid-induced[57] Smirnov-Zamkov reaction is the
result of a "1,3 addition" of a dimethylacetylenechloronium complex
to dimethylacetylene with a subsequent tautomeric shift and attack of
chloride ion to give XXXIII. These non-thermal cycloaddition reactions
have obvious synthetic utility but are beyond the scope of this chapter.
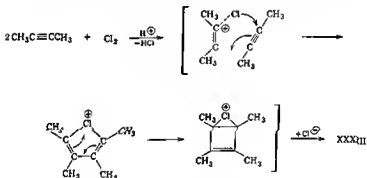
SCOPE AND LIMITATIONS

The number of reported thermal cycloadditions which form four-
membered rings is much smaller than the number reported for the similar
and much studied Diels-Alder reaction.[22, 40] The known principal classes
of substances which give successful *dimerization* reactions are included in
the following list.

Fluoro- and fluorochloro-alkenes having a double bond substituted
with a *gem*-fluoro group

Allenes

[56] Smirnov Zamkov, *Doklady Akad Nauk S S R*, **83**, 869 (1952) [*C A*, **47**, 2711 (1953)];
Smirnov Zamkov and Koutrennas, *Ukran Khim Zhur*, **21**, 233 (1955) [*C A*, **50**, 9392 (1956)]

[57] Criegee and Moschel, *Ann*, **92**, 2181 (1959)

[58] Reppe and co-workers, *Ann*, **560**, 1 (1948), Fraes and Boekelheide, *J Am Chem Soc*,
71, 4145 (1949), *Chapter Horrell and Schellenberg, Ber*, **92**, 139 (1959), Vogel, *Angew
Chem*, **66**, 305, 640 (1954), *Ann*, **615**, 14 (1958)

Ketenes (not covered in this chapter; see ref. 2).

Activated alkenes, dienes, and alkynes such as acrylonitrile, styrene, butadiene, and benzyne.

Cycloadditions involving two different alkenes or an alkene and an alkyne occur more or less well with the following combinations.
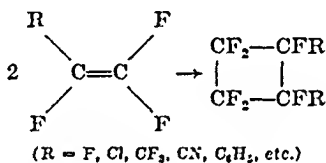
Fluoro- and fluorochloro-alkenes having a *gem*-fluoro substituted double bond with activated alkenes and alkynes, 1,3-dienes and allenes, and with ordinary alkenes. For the last group successful results have been reported so far only with tetrafluoroethylene.
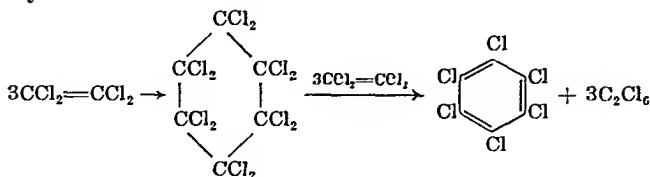
Allenes with activated alkenes and alkynes.

Ketenes with some activated alkenes, alkynes, and 1,3-dienes.

Each of the fundamental kinds of addends will be discussed separately.

Fluoro- and Fluorochloro-alkenes. A variety of fluoroalkenes of the following type have been found to dimerize in good yields at temperatures from 150° to 500° to give, apparently in all cases, the head-to-head

$$2 \quad \begin{array}{c} R \\ \diagdown \\ F \diagup \end{array} C = C \begin{array}{c} F \\ \diagup \\ \diagdown F \end{array} \rightarrow \begin{array}{c} CF_2\!\!-\!\!CFR \\ | \qquad | \\ CF_2\!\!-\!\!CFR \end{array}$$

$(R = F, Cl, CF_3, CN, C_6H_5, etc.)$

adducts under conditions where kinetic rather than thermodynamic control of the products obtains. 1,1-Dichloro-2,2-difluoroethylene also forms a dimer in high yield. Tetrachloroethylene does not behave in the same way. After twelve days at 300°, the only products identified besides unreacted tetrachloroethylene were hexachloroethane and hexachlorobenzene.[59] Presumably these products arise by way of dodecachlorocyclohexane, which acts as a chlorinating agent for tetrachloroethylene.

$$3CCl_2\!\!=\!\!CCl_2 \rightarrow \begin{array}{c} CCl_2 \\ \diagup \quad \diagdown \\ CCl_2 \quad CCl_2 \\ | \qquad | \\ CCl_2 \quad CCl_2 \\ \diagdown \quad \diagup \\ CCl_2 \end{array} \xrightarrow{3CCl_2=CCl_2} \begin{array}{c} Cl \\ Cl \diagup\diagdown Cl \\ | \qquad | \\ Cl \diagdown\diagup Cl \\ Cl \end{array} + 3C_2Cl_6$$

The general scope of the dimerizations of substituted fluoroalkenes is still undefined. A *gem*-fluoro group on the double bond appears to be very important, but other activation must also be supplied since vinylidene fluoride does not appear to dimerize to a cyclobutane.

[59] G. B. Kline and J. D. Roberts, unpublished research.

Tetrafluoroethylene adds well to a wide variety of multiple bonds.[19] Temperatures above 200° are usually required for simple alkenes, and 1-alkenes are more reactive than 2-alkenes. Activated alkenes like acrylonitrile react at much lower temperatures (~150°), while conjugated compounds like butadiene and vinylacetylene react at 100°. It is interesting and surprising that the double and triple bonds of vinylacetylene react at almost the same rate.

$$HC\equiv C-CH=CH_2 + CF_2=CF_2 \rightarrow$$

(approximately equal amounts)

With chloroprene or fluoroprene, tetrafluoroethylene gives mixtures of monocycloadducts. The two products XXXIV and XXXV are formed in about the same ratio for fluoroprene, while XXXIV is favored by 5:1 for chloroprene.[13] This result can be rationalized on the basis of the mechanistic considerations discussed earlier.

$$CF_2=CF_2 + CH_2=\overset{X}{\underset{(X=F,\ Cl)}{C}}-CH=CH_2 \rightarrow$$
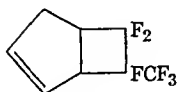
XXXIV   XXXV
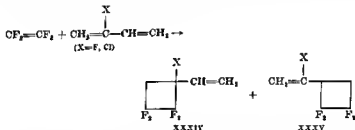
Six-membered ring compounds are not formed with fluoroalkenes and 1,3-dienes under conditions where kinetic control prevails. The only definite exception is the production of one part of 5,5,6,6-tetrafluorobicyclo[2.2.1]-2-heptene to two parts of the four-membered-ring cycloadduct with tetrafluoroethylene and cyclopentadiene.[23] The products from hexafluoropropene with cyclopentadiene and butadiene have been formulated as normal Diels-Alder products.[23] However, no compelling
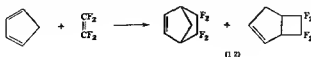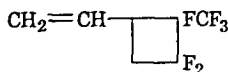

** McBee, Hsu, Pierce, and Roberts, *J. Am. Chem. Soc.*, 77, 915 (1955).

evidence was offered that the products are not actually XXXVI and XXXVII.

Conditions under which thermodynamic control of the products is exercised can be expected to lead to formation of six-membered-ring cycloadducts from fluoro- and fluorochloro-alkenes and 1,3-dienes because rearrangement of a variety of four-membered- to six-membered-ring adducts derived from such substances has been found to occur at 450–800°.[61]

Acetylene is reported to react with tetrafluoroethylene at 600° to give 1,1,4,4-tetrafluorobutadiene.[62] In this case the initially formed tetra-fluorocyclobutene undergoes thermal ring opening in the manner shown by cyclobutene itself.
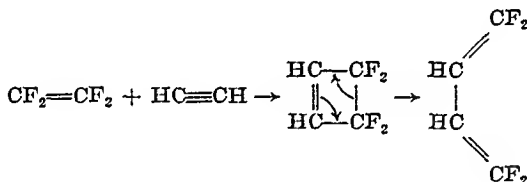

The fluorochloroalkenes with *gem*-fluorine atoms on the double bond usually add poorly, if at all, to the simple alkenes and alkynes but give excellent yields with 1,2- and 1,3-dienes and with reasonably activated alkenes and alkynes. If a poorly reactive addend is used, the fluoro-chloroalkenes undergo slow dimerization in competition with the desired cycloaddition. Vinylidene fluoride apparently does not add to styrene,[63] a fact which gives some indication of the degree of substitution required for facile addition. Likewise, it has been found that 1,2-difluoro-1,2-dichloroethylene does not add to phenylacetylene under conditions where 1,1-difluoro-2,2-dichloroethylene adds in 85% yields.[59] Symmetrical substitution in the addend may be undesirable. Thus diphenylacetylene gives no adduct with 1,1-difluoro-2,2-dichloroethylene[59] although, as mentioned, phenylacetylene adds readily.

[61] Drysdale, U.S. pat. 2,861,095 [*C.A.*, **53**, 9102 (1959)].

[62] Anderson, U.S. pat. 2,743,303 [*C.A.*, **51**, 465 (1957)].

[63] J. D. Roberts, unpublished research.

The head-to-head structures of the dimers of unsymmetrical fluorochloroethylenes have been proved by chemical means.[44-46]

$$(X = F, Cl)$$
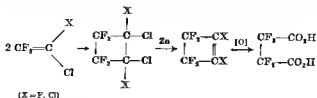
The mode of addition of trifluorochloroethylene and 1,1-difluoro-2,2-dichloroethylene to phenylacetylene, styrene, and 1-cyclohexenylacetylene has been established by degradation and interconversion reactions [28, 49]. In each case only one cycloadduct was formed, and its structure was in accord with predictions.

$$(X = F, Cl)$$

(Structure of cycloadduct XXXVIII proved by degradation[28])
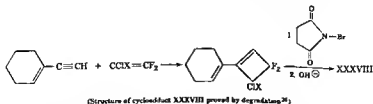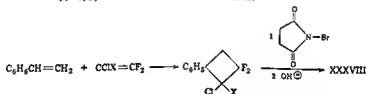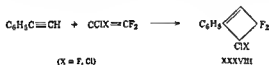
44 Harmon, U S pat 2,404,374 [C A., 40, 7234 (1946)].

45 Harmon, U S pat 2,436,142 [C.A., 42, 3779 (1948)].
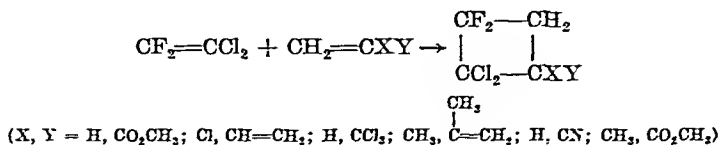
46 Henne and Ruh, J Am Chem. Soc., 69, 279 (1947), Henne and Zimmerscheid, ibid., 69, 281 (1947)

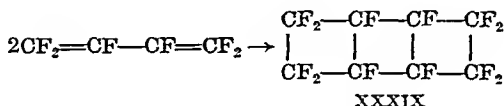47 Kropa and Padbury, Can pat 433,791 [C.A. 44, 2018 (1950)].

48 Kropa and Padbury, U S pat 2,590,019 [C.A., 46, 10197 (1952)]

49 C M Sharts, Doctoral Dissertation, California Institute of Technology, 1959
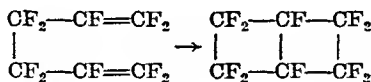
A study[70] of the cycloaddition reactions of 1,1-difluoro-2,2-dichloro-ethylene with various activated unsymmetrical alkenes and 1,3-dienes showed that only one compound was formed in each case. Although the structures of the products were not proved for each reaction, all the available data indicate that these adducts can be formulated as having the expected orientation.

$$CF_2{=}CCl_2 + CH_2{=}CXY \rightarrow \begin{array}{c} CF_2{-}CH_2 \\ | \qquad | \\ CCl_2{-}CXY \end{array}$$

$$(X, Y = H, CO_2CH_3;\ Cl,\ CH{=}CH_2;\ H,\ CCl_3;\ CH_3,\ \overset{\displaystyle CH_3}{\underset{\displaystyle |}{C}}{=}CH_2;\ H,\ CN;\ CH_3,\ CO_2CH_3)$$

Dimerization of perfluoro-1,3-butadiene has been reported to afford the unusual and interesting tricyclic substance XXXIX.[71]

$$2CF_2{=}CF{-}CF{=}CF_2 \rightarrow \begin{array}{c} CF_2{-}CF{-}CF{-}CF_2 \\ | \quad | \quad | \quad | \\ CF_2{-}CF{-}CF{-}CF_2 \end{array}$$
$$XXXIX$$

A similar structure has been written for the product of the intramolecular cyclization of perfluoro-1,5-hexadiene.[72]

$$\begin{array}{c} CF_2{-}CF{=}CF_2 \\ | \\ CF_2{-}CF{=}CF_2 \end{array} \rightarrow \begin{array}{c} CF_2{-}CF{-}CF_2 \\ | \quad | \quad | \\ CF_2{-}CF{-}CF_2 \end{array}$$

Perfluoro-2-butyne has been reported to give the tetramer XL,[73] but it now appears that the product is actually hexa(trifluoromethyl)benzene (XLI).[74]

$$CF_3C{\equiv}CCF_3 \longrightarrow$$

XLI

XL
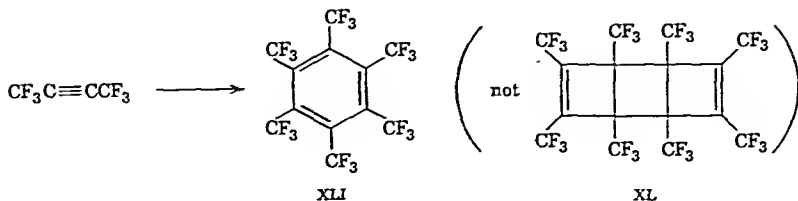
[70] G. N. B. Burch, Doctoral Dissertation, Ohio State University, 1949.
[71] Prober and Miller, *J. Am. Chem. Soc.*, **71**, 598 (1949).
[72] Fainberg and Miller, *J. Am. Chem. Soc.*, **79**, 4170 (1957).
[73] Brown, *J. Org. Chem.*, **22**, 1256 (1957). See also Ekstrom, *Ber.*, **92**, 749 (1959).
[74] Harris, Harder, and Sausen, *J. Org. Chem.*, **25**, 633 (1960); Brown, Gewanter, White, and Woods, *ibid.*, **25**, 634 (1960).

Pyrolyses of polymers of fluoro- and fluorochloro-ethylenes have been found to give cyclobutane derivatives.[27, 28, 73-77] Presumably these are formed by cycloadditions of the alkenes formed by degradation.

Allenes.   Lebedev[78] apparently was the first to observe the formation of cyclobutanes through dimerization of allenes. With allene itself, the product was reported to be 1,2-dimethylenecyclobutane, as expected from the diradical mechanism   At higher temperatures, in a flow system, the
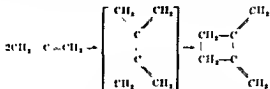
reaction appears to be less selective, and both the 1,2 and 1,3 adducts are formed in the ratio 85 15.[81] The over-all yield under these conditions is 50%.

Lebedev has reported that 1,1-dimethylallene dimerizes to give at least two of the three possible head-to-head products XLII-XLIV.[78] The predominant products were assigned structures XLII and XLIII.
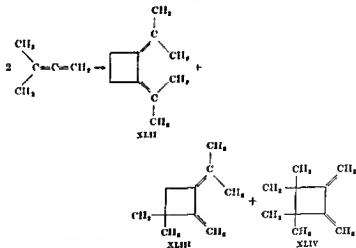
[73] Downing, Benning, and McHarness, U S pat 2,394,821 [C.A., 40, 1877 (1946)]

[74] Benning and Park, U S. pat 2,420,222 [C A. 41, 5891 (1947)]

[75] Downing, Benning, and McHarness, U S, pat 2,551,573 [C.A., 45, 9072 (1951)].

[76] Lebedev, J Russ Phys. Chem Soc., 43, 820 (1911) [C.A., 6, 478 (1912)].

Dimerization of 1,1-dimethyl-3-bromoallene affords XLV and XLVI in a ratio of 5:2.[79] Inspection of models suggests that hindrance between
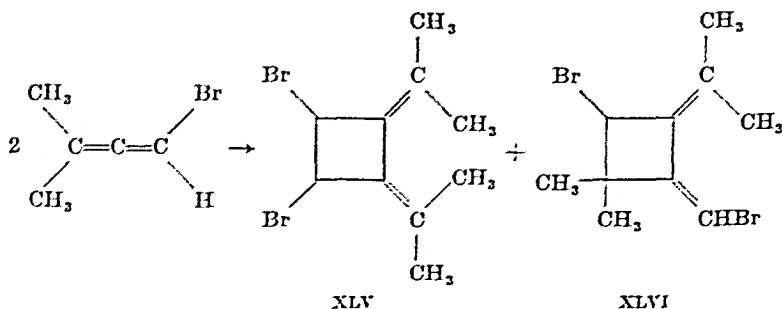
the methyl groups would make unlikely direct formation of XLII or XLV by way of a four-center transition state with the participating carbon atoms lying in one plane. Conceivably, the central carbon atoms could first be joined with the chains at or near right angles to one another, and then ring closure to the various possible products could take place by a partial rotation around the new C—C bond. Other mechanisms have been discussed by Petty.[79]
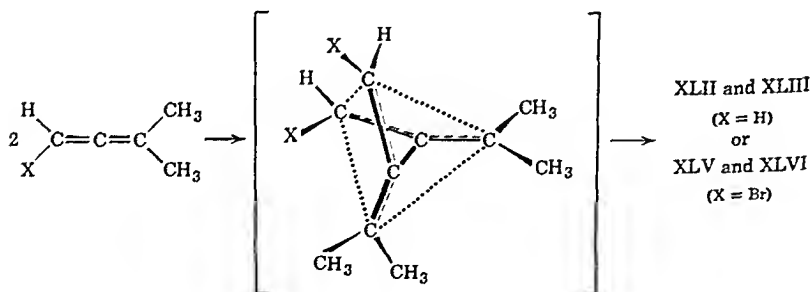
As mentioned earlier, the discovery that allene will undergo cyclo-addition with a variety of activated alkenes is of considerable synthetic importance for the preparation of 1,3-disubstituted cyclobutanes.[35,37] Generally there is concomitant formation of octahydronaphthalene derivatives from the allene dimer.[35,37,80] The reaction course with allene and acrylonitrile is typical.

[79] W. L. Petty, Doctoral Dissertation, University of California at Los Angeles, 1958.
[80] Alder and Ackermann, Ber., 87, 1567 (1954).
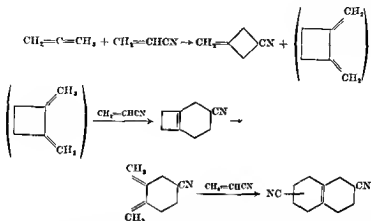
With unsymmetrical allenes and unsymmetrical alkenes, two different head-to-head cycloadducts can be formed. Although insufficient data are available for any final decision, it appears as though steric effects may be important in determining the product ratios. Thus comparison of the product ratios obtained with 1,1-dimethylallene and acrylonitrile[37] and methacrylonitrile[37] indicate a preference for formation of the product which has the smaller accumulation of adjacent methyl groups.

Addition of allene to acetylenes does not appear to work very satisfactorily. A yield of less than 1% of 1-phenyl-3-methylenecyclobutene was obtained from allene and phenylacetylene.[81]

Ketenes. A number of cycloadditions of ketenes and alkenes to form cyclobutanes has been reported. In general, the products have the structures predicted by the diradical mechanism. This contrasts strongly with ketene dimerizations,[2] in which the reported products always have the head-to-tail structures regardless of whether a cyclobutanedione or a β-lactone is formed. The dimerizations can be reasonably formulated as having important contributions to their transition states of the indicated ionic structures. It is possible that the apparent conformity of the additions of ketenes to alkenes to predictions based on the diradical

(a vinylaceto-β-lactone)

(a 1,3-cyclobutanedione)

mechanism is illusory. The difficulty is that all the substituted alkenes so far employed (e.g., styrene, cyclopentadiene, vinyl ethyl ether) would be expected to give the same product by either the diradical mechanism or an ionic process wherein the alkene acts as a *nucleophilic* agent. Clearly, further research is needed to establish the mechanism of the ketene cycloadditions so that prediction of the orientations of the products to be expected can be put on a firmer basis.

Most of the reported ketene additions have been carried out with diphenylketene, and it appears that this substance gives better results than ketene itself. Azibenzil (XLVIA) can be used as a convenient source of diphenylketene. Thus, with styrene in dioxane, azibenzil gives a 58%

[81] Applequist and Roberts, *J. Am. Chem. Soc.*, **78**, 4012 (1956).

yield of the cycloadduct [82] Diphenylketene appears to give cycloadducts even with unactivated alkenes such as cyclopentene[83] and cyclohexene.[83, 84]


$$C_6H_5-\overset{\overset{O}{\|}}{C}-\underset{\underset{N_2}{|}}{C}-C_6H_5 \xrightarrow{-N_2} [(C_6H_5)_2C=C=O] \xrightarrow{C_6H_5CH=CH_2}$$

(XLVI)
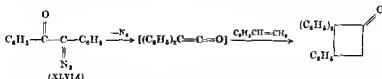
It adds also to ethoxyacetylene and similar substances in nitromethane at −20° to afford interesting cyclobutenones [85, 86]

$$(C_6H_5)_2C=C=O + HC\equiv COC_2H_5 \xrightarrow[-20°]{CH_3NO_2}$$
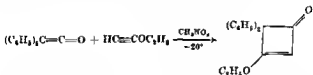
Ketene itself does not afford 3-phenylcyclobutenone when heated with phenylacetylene,[87] but it is now known[88] that the product is unstable under the reaction conditions.

Dimethylketene appears to be less reactive than diphenylketene, and adducts have been reported only with vinyl ethyl ether and cyclopentadiene.[89]

$$C_6H_5CH=CHCR + CH_2=C(OC_2H_5)_2 \longrightarrow$$
(R = C₆H₅CR=CH C₆H₅)
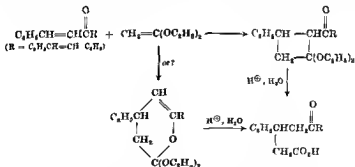
[82] Marvel and Kohan, *J Org Chem*, **16**, 741 (1951)

[83] Farmer and Farooq, *Chem & Ind (London)*, 1937, 1079   *J Chem Soc*, 1938, 1925

[84] Staudinger and Suter, *Ber*, **53**, 1092 (1920)

[85] Nieuwenhuis and Arens, *Rec trav chim*, **77**, 761 (1958)

[86] Nieuwenhuis and Arens, *Rec trav chim*, **77**, 1153 (1958)

[87] H E Simmons, E J Smutny, and J D Roberts, unpublished research.

[88] S L Manatt, Doctoral Dissertation, California Institute of Technology, 1959

[89] Staudinger and Meyer, *Helv Chim Acta*, **7**, 18 (1924)

Addition of allene to acetylenes does not appear to work very satisfactorily. A yield of less than 1% of 1-phenyl-3-methylenecyclobutene was obtained from allene and phenylacetylene.[81]

Ketenes. A number of cycloadditions of ketenes and alkenes to form cyclobutanes has been reported. In general, the products have the structures predicted by the diradical mechanism. This contrasts strongly with ketene dimerizations,[2] in which the reported products always have the head-to-tail structures regardless of whether a cyclobutanedione or a β-lactone is formed. The dimerizations can be reasonably formulated as having important contributions to their transition states of the indicated ionic structures. It is possible that the apparent conformity of the additions of ketenes to alkenes to predictions based on the diradical

$$2R_2C{=}C{=}O \rightarrow \begin{bmatrix} R_2\overset{\ominus}{C}{-}C{=}O \\ R_2C{=}\overset{\oplus}{C}{-}O \end{bmatrix} \rightarrow \begin{matrix} R_2C{-}C{=}O \\ | \quad | \\ R_2C{=}C{-}O \end{matrix}$$
$$\text{(a vinylaceto-}\beta\text{-lactone)}$$

$$\searrow \begin{bmatrix} R_2\overset{\ominus}{C}{-}C{=}O \\ O{=}\overset{\oplus}{C}{-}CR_2 \end{bmatrix} \rightarrow \begin{matrix} R_2C{-}C{=}O \\ | \quad | \\ O{=}C{-}CR_2 \end{matrix}$$
$$\text{(a 1,3-cyclobutanedione)}$$

mechanism is illusory. The difficulty is that all the substituted alkenes so far employed (e.g., styrene, cyclopentadiene, vinyl ethyl ether) would be expected to give the same product by either the diradical mechanism or an ionic process wherein the alkene acts as a *nucleophilic* agent. Clearly, further research is needed to establish the mechanism of the ketene cycloadditions so that prediction of the orientations of the products to be expected can be put on a firmer basis.

$$R_2C{=}C{=}O + CH_2{=}CHX \rightarrow \begin{bmatrix} R_2\overset{\ominus}{C}{-}C{=}O \\ H{-}\overset{\oplus}{C}{-}CH_2 \\ | \\ X \end{bmatrix} \rightarrow \begin{matrix} R_2C{-}C{=}O \\ | \quad | \\ H{-}C{-}CH_2 \\ | \\ X \end{matrix}$$

Most of the reported ketene additions have been carried out with diphenylketene, and it appears that this substance gives better results than ketene itself. Azibenzil (XLVIA) can be used as a convenient source of diphenylketene. Thus, with styrene in dioxane, azibenzil gives a 58%

[81] Applequist and Roberts, *J. Am. Chem. Soc.*, **78**, 4012 (1956).

earlier, are the cycloadducts from chlorinated ethylenes and hexachloro-cyclopentadiene with aluminum chloride.[54,55]

One of the most interesting means of formation of four-membered rings is through the apparent intermediacy of cyclobutadiene derivatives.[54,55] Thus Criegee[54] has demonstrated the formation of XLVII by treatment of the Smirnov-Zamkov[54] dichloride XXXIII with lithium amalgam, and Nenitzescu[55] has prepared XLVIII in a similar way. The generality of these reactions remains to be established.
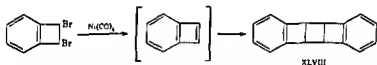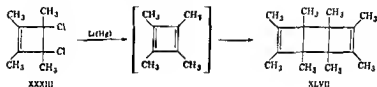
An interesting internal thermal cycloaddition has been reported by Wittig, Koenig, and Clauss[56]
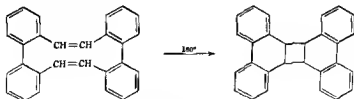
EXPERIMENTAL CONDITIONS

Comparison of Addend Reactivities. The vast majority of successful cyclobutane-forming cycloadditions involve as one or both addends a fluorinated alkene, an allene, a ketene, or a similarly activated alkene.

[54] Criegee and Louis, *Ber*, **90**, 417 (1957), Criegee, *Angew. Chem.*, **70**, 607 (1958)
[55] Avram, Dinu, and Nenitzescu, *Chem. & Ind. (London)*, 1959, 257.
[56] Wittig, Koenig, and Clauss, *Ann*, **593**, 127 (1955).

Ketene diethyl acetal is reported to add to dibenzalacetone and benzalacetophenone to form four-membered-ring cycloadducts.[90] However, the evidence for the structures of the products does not exclude the possibility that they actually contain six-membered rings.

Activated Alkenes. A number of alkenes carrying suitable activating groups has been reported to dimerize at various temperatures to give cyclobutane derivatives in low yields. Among the examples are butadiene,[45,46] acrylonitrile,[25] and 1,5-cycloöctadiene.[6] In general, the activating groups are the ones which would be expected to stabilize free radicals and, as discussed on p. 11, the dimerizations of unsymmetrical alkenes take place in the head-to-head manner.

Since most of the alkenes which dimerize to cyclobutanes also undergo thermal polymerization rather easily, it is usually necessary to have present an efficient polymerization inhibitor to cut down wastage of the monomer as a long-chain polymer. With styrene, iodine is effective and some 1,2-diphenylcyclobutane is formed.[91]

Tetracyanoethylene appears to have possibilities for formation of cyclobutane derivatives from suitable alkenes.[92] It adds to one of the double bonds of 1,2-diphenyl-3,4-dimethylenecyclobutene rather than in its usual 1,4 manner, which would give a cyclobutadiene derivative. It also adds to methylenecyclohexene to give a spiran.
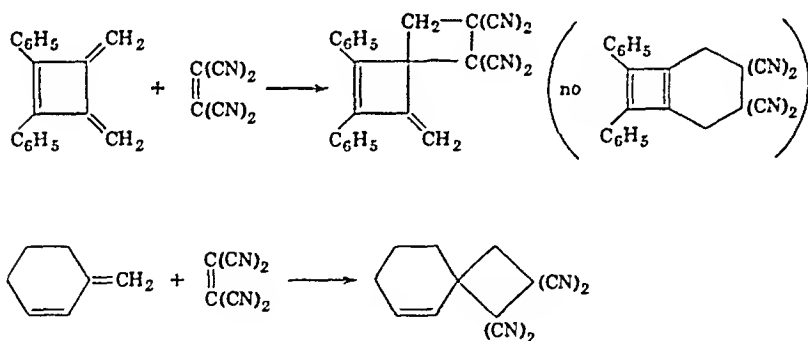
A few instances are reported of cyclobutane formation from substituted alkenes with the aid of ionic catalysts; e.g., 1,1-diphenylethylene is reported to be converted to a tetraphenylcyclobutane in low yield under the influence of dimethyl sulfate.[93] Other examples, which were mentioned

[90] McElvain and Cohen, *J. Am. Chem. Soc.*, **64**, 260 (1942).

[91] F. R. Mayo, private communication.

[92] Blomquist and Meinwald, *J. Am. Chem. Soc.*, **79**, 5316 (1957); **81**, 667 (1959).

[93] Belov and Lebedev, *J. Gen. Chem. (U.S.S.R.)*, **11**, 745 (1941) [*C.A.*, **36**, 446 (1942)].

Steel or other metallic autoclaves are potentially more hazardous than glass tubes, and equipment capable of withstanding operating pressures of 500 atm. is necessary if tetrafluoroethylene is used.[15] The hazards of allene cycloadditions have been pointed out,[25,27] and the use of an inert solvent as a diluent to diminish the possibility of violent decomposition is recommended

Addition reactions with fluoroalkenes in metal vessels may also be hazardous. For example, the addition of trifluorochloroethylene to 1-cyclohexenylacetylene in a 1-l. stainless steel Parr bomb was carried out twice without difficulty, but in a third run the head gasket ruptured and the bomb was ruined by the reaction of the expanding hot gases with exposed stainless steel surface[43]

EXPERIMENTAL PROCEDURES

1,1,2,2-Tetrafluoro-3,3,4,4-tetrachlorocyclobutane.[25] Four hundred grams of 1,1-difluorodichloroethylene was agitated at 200° for 12 hours in a stainless steel bomb. The unchanged monomer (75 g.) was recovered by distillation. The residue was taken up in ether and then distilled to give 313 g. of crystalline dimer: b.p. 131–132° and m.p. 84.8°. The conversion was 80%, and the yield 92%.

1,1-Difluoro-2,2-dichloro-3-phenylcyclobutene.[28] A mixture of 18.4 g. (0.18 mole) of phenylacetylene, 24.9 g. (0.18 mole) of 1,1-difluoro-2,2-dichloroethylene, and 0.1 g. of hydroquinone was heated in a sealed glass tube at 130° for 2 hours. The crude product was flash-distilled under reduced pressure to remove some polymeric material and then fractionated through a 10-cm. Vigreux column. The yield of 1,1-difluoro-2,2-dichloro-3-phenylcyclobutene was 30.1 g. (71%), b.p. 109–111°/5 mm., n_D^{25} 1.5435.

1,1,2-Trifluoro-2-chloro-3-(1′-cyclohex-1-enyl)cyclobutene.[49] To each of four heavy-walled Pyrex tubes (19 × 25 × 615 mm.) was added 25.0 ml. (22.0 g., 0.208 mole) of 1-cyclohexenylacetylene. The tubes were cooled in a bath of isopropyl alcohol and solid carbon dioxide, and trifluorochloroethylene was passed in until 25 ml. (about 37 g., 0.32 mole) of liquid trifluorochloroethylene collected. The tubes were then sealed, allowed to warm to room temperature, and heated over a 4-hour period to 95°. After 20 hours at 95°, the tubes were cooled to room temperature and then to –78°, opened, and the excess trifluorochloroethylene allowed to escape as the material warmed to room temperature (hood). The crude adducts were combined and distilled through a Claisen flask under reduced pressure to give 149 g. (79%) of 1,1,2-trifluoro-2-chloro-3-(1-cyclohex-1-enyl)cyclobutene, b.p. 71–73°/1 mm., n_D^{25} 1.4808. When cooled, the product crystallized as sharp white needles of m.p. 11–13°.

For convenience, we shall call these "primary" addends. Primary addends can usually be added to one another and also undergo cycloaddition with a variety of substituted alkenes, alkynes, conjugated dienes, and enynes. The latter substances can be called "secondary" addends, and among them are many of the usual Diels-Alder dienes and dienophiles. In general, the ease of reaction of the secondary addends decreases in the order: conjugated dienes and enynes > unsymmetrically substituted alkenes > symmetrically substituted alkenes. Among the primary addends, the fluoroalkenes appear to react more readily than allenes. Although the number of reported ketene cycloadditions is too small to permit much generalization, ketenes seem to add to alkenes under milder conditions than those commonly used for adding fluoroalkenes to alkenes.

Reaction Conditions. Most cycloadditions are carried out at 100–225° under autogenous pressure of reactants in sealed glass tubes or steel autoclaves. Solvents are usually not beneficial but are sometimes recommended for safety reasons. It is common to use a polymerization inhibitor such as hydroquinone or terpene B,[19] but this is probably only of psychological value in the absence of important competing free-radical thermal polymerization reactions. As inhibitors do not appear to affect the *cycloaddition* reaction, inclusion of an inhibitor is unlikely to be positively harmful. Exclusion of oxygen may be generally desirable; but, except for a few instances where tetrafluoroethylene[19] and other monomers subject to oxygen-initiated polymerization have been employed, it does not seem to be customary practice to degas the reactants.

Safety Precautions. Low-molecular-weight fluorinated alkenes, ketenes, and allenes are usually gases at room temperature. Consequently it is desirable to use a well-ventilated area for handling the reactants—particularly because tetrafluoroethylene, trifluorochloroethylene, and ketene may present toxicity hazards comparable to or even greater than those of phosgene. Fluorinated alkenes and their cycloadducts should be handled with care, especially if there is a possibility of the presence (even in trace amounts) of certain olefins that contain fluorine linked to the doubly bonded carbon atoms. Fluorinated olefins generally should be regarded as highly toxic materials. Perfluoroisobutylene in particular is a deadly poison and exerts its effects in an insidious manner without warning. Perfluoroisobutylene is known to arise from thermal transformations of tetrafluoroethylene and polytetrafluoroethylene.

The usual precautions should be taken with reactions run in sealed glass tubes. After a reaction is complete, sealed tubes should be allowed to cool and should be vented before handling to remove hydrogen fluoride, hydrogen chloride, or other gases which often form in reactions involving fluoro- and fluorochloro-alkenes.

of fluoroalkenes are discussed before those of allene, the reaction of tetra-fluoroethylene with allene is listed with the fluoroalkene adducts. The arrangement of compounds within any given table follows that of Beilstein. Familiarity with arrangement of the Beilstein volumes and the difference between "functioning" and "non-functioning" derivatives will permit any compound to be found quickly. The arrangement has the advantages of being specific and usually leading to close listings for similar compounds.

3-Methylenecyclobutanecarbonitrile.[37]   A 500-ml. stainless steel rocker bomb was charged with 212 g. (4 moles) of acrylonitrile, 40 g. (1 mole) of allene, and 2 g. of hydroquinone.   The bomb was heated at 200° with agitation for 10.5 hours.   The bomb was allowed to cool to room temperature, opened, and the contents distilled.   After 120.4 g. of unreacted acrylonitrile, there was obtained 55.4 g. (60.4%) of 3-methylene-cyclobutanecarbonitrile, b.p. 64–65°/21 mm., n_D^{25} 1.4595.   The distillation flask contained 32.5 g. of a tan solid residue, m.p. 138–143°.   Several recrystallizations from acetone followed by one recrystallization from isopropyl alcohol gave white needles of 1,2,3,4,5,6,7,8-octahydronaphthalene-2,6-(and/or 2,7)-dicarbonitrile, m.p. 143.5–144.5°.

It may be generally advisable to run reactions of this type with an inert solvent as diluent even though the yields may be somewhat lower.[36, 37]

Bicyclo-[3.2.0]-2-hepten-6-one.[97]   Approximately   0.65 mole   of ketene was absorbed in a mixture of 50 ml. of toluene and 0.65–0.70 mole of freshly distilled cyclopentadiene contained in a bomb cooled by a solid carbon dioxide-isopropyl alcohol mixture.   The sealed bomb was heated at 100° for 2 hours* and then cooled to room temperature.   The reaction mixtures from three such runs were combined, and on distillation (in a hood) 105 g. of crude ketone, b.p. 145–185°, was obtained.   The impure ketone was purified through its semicarbazone.   From 105 g. of crude ketone there was obtained 56 g. (17.4% based on ketene) of semicarbazone, m.p. 216.0–219.5°.   After two recrystallizations from methanol-water (3:1), it melted at 219.0–220°.

The pure ketone, b.p. 62.0–63.5°/20 mm., n_D^{20} 1.4819, could be obtained in 85% yield by decomposition of the semicarbazone with phthalic anhydride and water.

2,2,3-Triphenylcyclobutanone.[84]   Equimolar portions of diphenylketene (8.0 g.) and styrene (4.5 g.) were heated in a sealed tube for 24 hours at 60°.   The crude solid addition product crystallized as white needles from ethanol, m.p. 135–136°.   The yield was 11.5 g. (93%).

TABULAR SURVEY

Tables I through IV include cycloaddition reactions classified according to primary addend and reported to June, 1959.[93]   An "early-position" principle was used in arranging the tables.   Thus, since cycloadditions

[97] Blomquist and Kwiatek, *J. Am. Chem. Soc.*, **73**, 2098 (1951).

* It is recommended that reactions of this type be carried out behind a suitable barricade.

[93] A rather large number of tetrafluoroethylene cycloadditions have been disclosed by Barrick, U.S. pat. 2,462,347 [*C.A.*, **43**, 4294 (1949)], but no yields or physical properties are cited for the products of many of them.   Only the examples for which Barrick gives yields and physical properties are included in the tables.

1-Octadecene	CH₃(CH₂)₁₅CHClCF₂CF₂CH₃ (25)	—	None	283–305	8		101
Acetylene	CF₂=CH—CH=CF₂ (—)	—	None	600	4		62
Allene	CH₂=CCF₂CF₂CH₂ (14)	1.00	None	150	8		19
	(17)	1.00	None	150	14		98
1,3-Butadiene	CH₂=CHCHClCF₂CF₂CH₃ (90)	0.43	None	100–125	8		19
			None	100	12		98, 99
2-Fluoro-1,3-butadiene	CH₂=CFClCF₂CF₂CH₃ (35)	0.54	None	100–125	8		19
2-Chloro-1,3-butadiene	CH₂=CClCClCF₂CF₂CH₃ (51)	1.00	None	100	9.75		19, 08, 00
	CH₂=CClCHClCF₂CF₂CH₃ (10)		None		8		19
			None		9		09
1,3-Pentadiene	CH₃CH=CHCHClCF₂CF₂CH₃ (68)	1.00	None	100–125	8		10
	(—)		None	100	9		09
2-Methyl-1,3-butadiene	CH₂=CClCH=CHCF₂CF₂CH₃ (83)	1.00	None	100–125	8		10
	(—)		None	125	11.25		08, 00
Vinylacetylene	HC≡CCHClCF₂CF₂CH₃ (35)	1.00	None	100	16		19, 08, 09
	CH₂=CH—C=CHClCF₂CF₂ (35)						
	CH₃CF₂CH=CHClCF₂CF₃ (3,6)						
	C₂H₅CHClCF₂CF₂CH₃ (5,5)	1.04	None	100	16		19, 08, 09

Note: References 99 to 127 are on p. 58.

* The yield is based on the aldehol used in smaller molal amount.
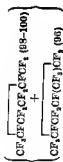† This is the ratio of the first-named addend to the second.
‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 0.

TABLE I

Cyclobutanes from Thermal Cycloaddition Reactions of Fluoro- and Fluorochloro-alkenes

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
Tetrafluoroethylene						
Ethylene	$CF_2CF_2CH_2CH_2$ (40)	0.13	None	200	7.5	19, 99
Tetrafluoroethylene	$CF_2CF_2CF_2CF_2$ (—)	—	None	200	13	64
Vinyl chloride	$CF_2CF_2CH_2CHCl$ (23)	0.24	None	150	8	19, 99
	(11)	1.0	Gas	408–526	Flow system	99
Trifluorochloroethylene	$CF_2CF_2CF_2CFCl$ (40)	0.84	None	150	13	100
1,1-Dichloroethylene	$CF_2CF_2CH_2CCl_2$ (40)	0.39	None	150	8–12	19, 99
Trichloroethylene	$CF_2CF_2CCl_2CHCl$ (18)	0.79	None	225	8	19
Propylene	$CH_2CHCF_2CF_2CH_2$ (72)	0.17	None	225	9	19, 99
Allyl chloride	$CF_2CF_2CH_2CHCH_2Cl$ (42)	0.30	None	150	8, 9.5	19, 99
2-Butene	$CH_2CHCF_2CF_2CHCH_3$ (5)	0.22	None	150	8, 9.5	19, 99
Isobutylene	$(CH_3)_2CCF_2CF_2CH_2$ (30)	0.22	None	175	7.75	19, 99
Methallyl chloride	$CF_2CF_2CH_2C(CH_3)CH_2Cl$ (45)	0.34	None	225	8.25	19, 99
$CH_2(CH_2)_nCH{=}CH_2$ (n = 11–19)	$CH_2(CH_2)_nCHCF_2CF_2CH_2$ (—) (n = 11–19)	~1.0	None	150	8, 6.3	19, 99
1-Tetradecene	$CH_3(CH_2)_{11}CHCF_2CF_2CH_2$ (35)	—	None	200–315	8	101
			None		—	101

$CH_2CF_2CF_2CH$ $(CH_2)_n$ ($n = 10-13$) $CH_2=CH$		—		—	104
$CH_2CF_2CF_2CH$ $(CH_2)_n$ ($n = 10-14$) Camphene		None		210–310	19
CH_3 CH—CH_2—CH $(CH_2)_{10}CH_2$ (7)	1.00	None	150		10
Cyclopentadiene (see Dicyclopentadiene)					
1,3-Cyclohexadiene CH_2=CHCH$_2$CH$_2$,CHClCHClCF$_2$CF$_2$ (50)	2.00	None	100	100–125	8 10
Dicyclopentadiene CH_2CH=CHCHClCF$_2$ $C_4F_7 \cdot C_4H_7Cl$ (0)	2.00	None	100	8	19
CH_2CH_2=CHClCHClCF$_2$CF$_2$CF$_2$H (47) CH | CH | CF_2 | CH_2J (23) CH | CH | CF_2 | CH	2.00	Gas	470–480	Flow system	33

Note: References 90 to 127 are on p. 55.

* The yield is based on the added used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in the column.

TABLE I—*Continued*

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES

Tetrafluoroethylene (Continued)

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
Methyl vinyl ether	CF₂CF₂CH₂CHOCH₃ (13)	0.23	None	150	8–9.5	19, 99
Allyl alcohol	CF₂CF₂CH₂CHCH₂OH (45)	0.23	None	150	8	19
Dimethallyl ether	CF₂CF₂CH₂C(CH₃)CH₂OCH₂C(CH₃)=CH₂ (20)	0.42	None	100–125	8	19, 99
Acrolein	CF₂CF₂CH₂CHCHO (12)	0.22	None	150	8	19, 99
Methacrolein	CF₂CF₂CH₂C(CH₃)CHO (50)	0.28	None	150	8	19, 99
Methyl vinyl ketone	CF₂CF₂CH₂CHCOCH₃ (18)	0.28	None	150	8	19, 99
Vinyl acetate	CF₂CF₂CH₂CHOCOCH₃ (27)	0.34	None	150	8–13	19, 99
Acrylonitrile	CF₂CF₂CH₂CHCN (84) (58)	0.39 0.50	None None	150 125	8 17	19, 99, 102 103
Methyl α-chloroacrylate	CF₂CF₂CH₂CClCO₂CH₃ (21)	0.00	None	150	8	19
Vinylacetonitrile	CF₂CF₂CH₂CHCH₂CN (15) (—)	0.27 —	None None	150 125	8 17	19, 99 103
Methyl methacrylate	CF₂CF₂CH₂C(CH₃)CO₂CH₃ (84)	0.80	None	150	8–12	19, 99
Methacrylonitrile	CF₂CF₂CH₂C(CH₃)CN (—)	—	None	125	17	103

Isopropenylacetylene HC≡C(CH₃)CH=CH₂ (25)	2.9	None	95	24	69
$\underset{\text{H}_2\text{C=C(CH}_3)_2\text{O}—\text{CH=CHCF}_2\text{CHCl}}{}$ (18)					
CH₃CF₂CFClCH(CH₃)₂—CHCF₂CFCl (P) (16)					
Ethyl acrylate CF₂CF₂CH₂CHCO₂C₂H₅ (50)	>1	None	180	24	109
Acrylonitrile CF₂CF₂CH₂CHCN (—)	†	None	150	8	102
Ethyl propiolate CF₂CF₂CH=CCO₂C₂H₅ (29)	>1	None	180	24	109
1-Cyclohexenylacetylene C₆H₉CH=CHCF₂CF₂ (70-90)	1.01	None	95	24	80
Styrene C₆H₅CH(CH₂CF₂)₂CFCl (71)	1.14	None	120	23	27
Phenylacetylene C₆H₅C=CHCF₂CF₂ (70)	1.01	None	120	24	29, 105
1,1-Difluoro-2,2-dichloroethylene	—	None	—	—	64
1,1-Difluoro-2,2-dichloro-ethylene CF₂CCl₂CF₂CF₂ (—) (80-85) (99)	††	None None	200 200	12 5-6	93 100
3,3,3-Trichloropropene CCl₃CH₂CHCF₂CF₂ (18)	1.03	None	131-135	19	70

Note: References 99 to 127 are on p. 50.

* The yield is based on the added metal used in smaller molal amount.

† This is the ratio of the first-named addend to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column d.

TABLE I—*Continued*

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES
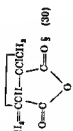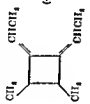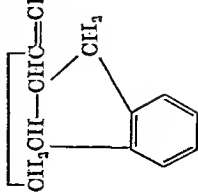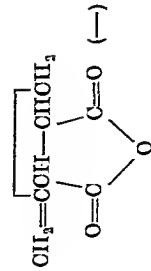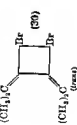
Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
Tetrafluoroethylene (Continued)						
Styrene	$C_6H_5CHCF_2CF_2CH_2$ (85)	0.42	None	175	13	19, 99
Phenylacetylene	$C_6H_5C=CHCF_2CF_2$ (—)	—	None	—	—	105
3,4-Epoxy-1-butene	$CF_2CF_2CH_2CHCHCH_2O$ (9)	1.32	None	135	10	19
2-Vinylfuran	$CF_2CF_2CH_2CHC$—$CHCH=CHO$ (77)	0.38	None	150	8	19, 99
Safrole	$CH_2O_2C_6H_3CH_2CHCF_2CF_2CH_2$ (18)	1.03	None	150	8	19
Trifluorochloroethylene						
Trifluorochloroethylene	$CF_2CFClCFClCF_2$ (64) (*cis* and *trans*)	—	None	200	11	64, 65
	(80)	—	None	200	8	66
	(—)	—	None	200	5–6	106
	(59)	—	None	220	12	107
	(<20)	—	Gas	680–760	Flow system	107
	(11)	—	Gas	550	Flow system	108
1,1-Difluoro-2,2-dichloro-ethylene	$CClFCF_2CF_2CCl_2$ (32)	1.13	None	200	18.5	67, 68

Reactants	Molar ratio †	Pressure ‡	Temp. (°C)	Time (hr.)	References
Perfluoropropylene $\{\,CF_2CFCF_2CFCF_2CF_3$ (88–100) $CF_2CFCF(CF_2)CF_2CF_3$ (90) $\,\}$ with CF_3	—	None	250–450	19–24	40
Perfluoropropylene	—		400	18	73
1,3-Butadiene $CF_2\|$ $CH_2{=}CHCH{=}CH_2$ (84)	1.1	None	160	24	60
Cyclopentadiene (98–99) F_2 CF_2	1.0–1.25	None	135–180	24–60	60
Perfluoro-1,3-butadiene $CF_2{=}CFCF{=}CF_2CF{=}CF_2$ (—) $CF_2{-}CF{=}CF{-}CF_2$ (69) $CF_2{-}CF{=}CF{-}CF_2$	—	Gas	150	44	71, 111
Perfluoro-1,5-hexadiene $CF_2{-}CF{-}CF_2{-}CF_2$ (—) $CF_2{-}CF{=}CF{-}CF_2$	—		500	Flow system	71, 111
Perfluoro-1,3-hexadiene $CF_2{-}CF_2{-}CF_2$ (70) $CF_2{-}CF{=}CF{-}CF_3$	—	None	450	Flow system	72

Note: References 99 to 127 are on p. 56.
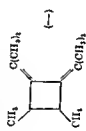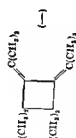
* The yield is based on the smaller metal amount.
† This is the ratio of the first-named added to the second.
‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.
§ This structure is based on mechanistic considerations and any available chemical evidence.
‖ A different structure was assigned by the original investigators.

TABLE I—*Continued*

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
1,1-*Difluoro-2,2-dichloroethylene* (*Continued*)						
2-Chlorobutadiene	CCl₂CF₂CH₂CClCH=CH₂ § (90) + CCl₃CF₂CH₂CHC(Cl)=CH₂ (?)	1.17	None	97–112	5.5	70
		—	—	—	—	
2,3-Dimethyl-1,3-butadiene	CCl₂CF₂CH₂C(CH₃)C(CH₃)=CH₂ § (68)	1.00	None	96–115	5.5	70
2-Methyl-1-penten-3-yne	CCl₂CF₂CH₂C(CH₃)C≡CCH₃ (63) CCl₂CF₂CH=CC(CH₃)=CH₂ § (?)	0.02	None	140	70	110
Methyl acrylate	CCl₂CF₂CH₂CHCO₂CH₃ § (48)	1.01	None	130 then 170	19 20	70
Acrylonitrile	CCl₂CF₂CH₂CHCN (49)	0.98	None	133–139	20	70
Methyl methacrylate	CCl₂CF₂CH₂C(CH₃)CO₃CH₃ § (74)	0.7	None	130–139	20.4	70
Styrene	C₆H₅CHCH₂CF₂CCl₂ (58)	1.01	None	130	3	27
Phenylacetylene	C₆H₅C=CHCF₂CCl₂ (71) (58)	1.00 0.88	None None	130 95	2 48	26 110

TABLE II

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF ALLENES

Addenda	Product (Yield, %)*	Mole Ratio†	Temp., °C‡	Solvent	Time, Hours	Refs
Allene						
Allene	$CH_2=CC(=CH)CH_2CH_2CH_2$ (50)	—	500–510	Gas	4–6 sec	114
	(5)	—	140–150	None	82	9
	(43)		400	None	Flow system	24
	$CH_2=CCH_2C=CH_2CH_2CH_2$ (7)					
Methacrolein	$CH_2=CCH_2CH(CHO)CH_2CH_2$ (0.7)	0.5	200	Benzene	8	35, 37
Acrylic acid	$CH_2=CCH_2CH_2CH(CO_2H)CH_2$ (21)	0.5	200	None	6	35, 37
Methyl acrylate	$CH_2=CCH_2CH_2CH(CO_2CH_3)CH_2$ (23)	0.23	200	None	13	35, 37
Acrylonitrile	$CH_2=CCH_2CH_2CH(C≡N)CH_2$ (69)	0.25	200	None	10.5	35, 37
	(57)	0.63	200–270	Toluene	4	38
Methyl methacrylate	$CH_2=CCH_2CH_2C(CH_3)(CO_2CH_3)CH_2$ (25)	0.5	200	None	8	35, 37
Methacrylonitrile	$CH_2=CCH_2CH_2C(CH_3)(C≡N)CH_2$ (62)	0.17	225	None	12	35, 37

Note. References 99 to 127 are on p. 56.

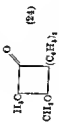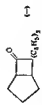* The yield is based on the addend used in smaller molal amount.
† This is the ratio of the first-named addend to the second.
‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

TABLE I—*Continued*

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF FLUORO- AND FLUOROCHLORO-ALKENES

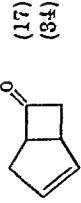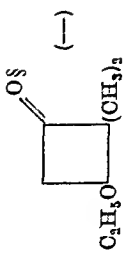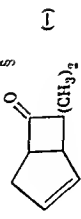| Addenda	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
Perfluoroacrylonitrile						
1,3-Butadiene	CF₂——CFCN / CH₂——CHCH=CH₂ (88)	0.75	None	40–50	8	112
Perfluoroacrylonitrile	NCCFCF₂CF₂CFCN (100)	—	None	230	72	112
α,β,β-Trifluorostyrene						112
α,β,β-Trifluorostyrene	C₆H₅CFCF·CF₂CFC₆H₅ (15)	—	—	—	—	113

Note: References 98 to 127 are on p. 56.

* The yield is based on the addend used in smaller molal amount.
† This is the ratio of the first-named addend to the second
‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

Reagent	Structure					
Chloromaleic anhydride	CH₂=CCl—COCH₃ ; O=C-O-C=O (30)	0.33	200	Benzene	5	35, 37
4-Vinylpyridine	CH₂=CCH(C₅H₄N)CH₃ (23)	1.0	200	Benzene	8	35
1,2-Dimethylallene	(—) structure	—	150	None	—	115
1,3-Dimethylallene	(—) structures	(—)	—	—	—	
1,1-Dimethylallene	structures	(—)	130	None	—	78

Note: References 59 to 127 are on p. 56.

* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named aldehyd to the second.

‡ Autogenous pressure is to be understood, except where a flow system is indicated in column *a*.

§ This structure is based on mechanistic considerations; a less likely alternative is CH₂=CCOCl|ClCH₃ ; O=C-O C=O

TABLE II—Continued

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF ALLENES

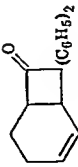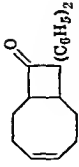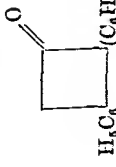| Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp, °C‡	Time, Hours	Refs.
Allene (Continued)						
α-Acetoxyacrylonitrile	$CH_2=COH_2C(CN)(OCOCH_3)CH_2$ (20)	0.5	Benzene	200	6	35, 37
Diethyl fumarate	$CH_2=CCH(CO_2C_2H_5)CH(CO_2C_2H_5)CH_2$ (11)	0.5	None	200	8	35, 37
Diethyl itaconate	$CH_2=COH_2C(CO_2C_2H_5)(CH_2CO_2C_2H_5)CH_2$ (32)	0.38	None	225	8	35, 37
Styrene	$CH_2=CCH_2CH(C_6H_5)CH_2$ (22)	1	Benzene	200	4	35, 37
α-Methylstyrene	$CH_2=CCH_2C(CH_2)(C_6H_5)CH_2$ (20)	0.67	None	190	4	35, 37
Phenylacetylene	$CH_2=CCH=C(C_6H_5)CH_2$ (<1)	1.2	None	150	24	81
Indene	$CH_2CH—CHC=CH_2$ structure with CH_2 (28)	0.33	None	200	8	35, 37
Maleic anhydride	$CH_2=COH—CHOH$ anhydride structure (—)	0.50	Benzene	200	8	35, 37

1,1-Dimethyl-3-bromo-allene	(59) $(CH_3)_2C$ — Br, Br structure (meso)	None	60–80	—	70
Trimethylallene	(12) $(CH_3)_2C$ — Br, BrHC, $C(CH_3)_2$ structure	None	150	—	115
Trimethylallene	Mixture containing CH_3, $C(CH_3)_2$, CH_3 structure	(–)	150	—	115
Tetramethylallene	$(CH_3)_2C$ — $C(CH_3)_2$ structure	(–)	150	Various	116
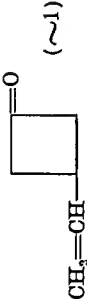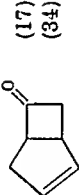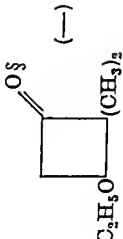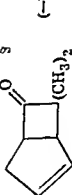
Note: References 99 to 127 are on p. 56.

* The yield is based on the addend used in smaller molal amount.
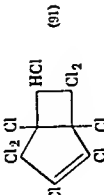† This is the ratio of the first-named addend to the second.
‡ Autogenous pressure is to be understood, except where a flow system is indicated in column 6.

TABLE III

Cyclobutanes from Thermal Cycloaddition Reactions of Ketenes

Addends Ketene	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
1,3-Butadiene	(~1)	0.25	None	100	2	35
Cyclopentadiene	(17) (34)	1.0 0.8	Toluene Toluene	100 100	2 1	97 117
1,3-Cyclohexadiene	(5)	1.2	Toluene	100	4	97
Dimethylketene						
Ethyl vinyl ether	(—)	1.0	None	−20	72–96	89
Cyclopentadiene	(—)	0.03	None	−20	12	89

Diphenylketene

Structure (yield)	Addend	Ratio[‡]	Solvent	Temp.		Yield[*]
C_2H_5O O $(C_6H_5)_2$ (60)	Vinyl ethyl ether	0.91	None	60	24	84
C_2H_5O O $(C_6H_5)_2$ (35)	Ethoxyacetylene	0.73	CH_3NO_2	−20	170	86
H_3C CH_3O O $(C_6H_5)_2$ (24)	1-Methoxypropyne	0.73	Benzene	60	3.5	88
H_3C C_2H_5O O $(C_6H_5)_2$ (80) (54)	1-Ethoxypropyne		Benzene CH_3NO_2	−20 −20		86 80
O $(C_6H_5)_2$	Cyclopentene					118
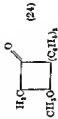
Note: References 99 to 127 are on p. 56.

[*] The yield is based on the addend used in smaller molal amount.

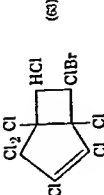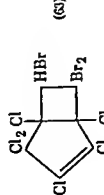[‡] This is the ratio of the first-named addend to the second.

[†] Autogenous pressure is to be understood.

[§] This structure is based on mechanistic considerations and any available chemical evidence.

TABLE III

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF KETENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
Ketene						
1,3-Butadiene	(~1)	0.25	None	100	2	35
Cyclopentadiene	(17) (34)	1.0 0.8	Toluene Toluene	100 100	2 1	97 117
1,3-Cyclohexadiene	(5)	1.2	Toluene	100	4	97
Dimethylketene						
Ethyl vinyl ether	(—)	1.0	None	−20	72–96	89
Cyclopentadiene	(—)	0.03	None	−20	12	89

Diphenylketene

Vinyl ethyl ether	(80)	0.91	None	59	24	84
Ethoxyacetylene	(35)	0.73	CH$_3$NO$_2$	~20	170	88
1-Methoxypropyne	(24)	0.73	Benzene	60	3.5	86
1-Ethoxypropyne	(80) (54)	| |	Benzene CH$_3$NO$_2$	-20 -20	| |	86 86
Cyclopentadiene						118

Note: References 99 to 127 are on p. 55.

* The yield is based on the adduct used in smaller molal amount.
† This is the ratio of the first-named addend to the second.
‡ Autogenous pressure is to be understood.
§ This structure is based on mechanistic considerations and any available chemical evidence.

TABLE III—Continued

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF KETENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
Diphenylketene (Continued)						
Cyclohexene	(50)	1.0	None	100	240	83, 84
Cyclopentadiene	(40)	0.33	Pet. ether	Room	48	84,110,120
	(92)	0.33	Pet. ether	Room	24	121
	(62)	0.04	Pet. ether	Room	48	15
	(85)	—	—	—	—	83
1,3-Cyclohexadiene	(—)	1.0	None	Room	12	83
1,5-Cycloöctadiene	(80)	1.20	None	60	2	0
Styrene	(93)	1.0	None	40	24	84,120,122
	(0–58)	1.0‖	Dioxane	Reflux	1–96	82

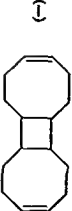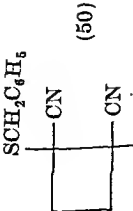|					
p-Chlorostyrene (82) p ClC₆H₄	1.0	None	60	24	84
p-Methylstyrene (81) p CH₃C₆H₄	1.0	None	60	24	84
Phenylacetylene (—)	—	—	—	—	121
p-Methoxystyrene (84) p CH₃OC₆H₄	1.0	None	60	24	84

Note: References 99 to 127 are on p. 58.

* The yield is based on the aldend used in smaller molal amount.
† This is the ratio of the first-named aldend to the second.
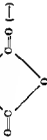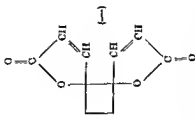‡ Autogenous pressure is to be understood.
§ This structure is based on mechanistic considerations and any available chemical evidence.
‖ Arshenal was used as a source of diphenylketene (see p. 99).
¶ A different structure was assigned by the original investigators.

TABLE IV

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF ACTIVATED ALKENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
Trichloroethylene						
Hexachlorocyclopentadiene	(structure) (91)	1.0	None, $AlCl_3$ present	80	2	54, 55
1,2-Dichlorobromoethylene						
Hexachlorocyclopentadiene	(structure) (63)	1.0	None $AlCl_3$ present	75–78	2	54
Tribromoethylene						
Hexachlorocyclopentadiene	(structure) (63)	1.0	None, $AlCl_3$ present	20–80	2	54
1,3-Butadiene						
1,3-Butadiene	CH_2=CHCHCH$_2$CH$_2$CHCH=CH$_2$ (4–5) (*trans*)	—	None	150	18	45
Vinylacetylene						
Vinylacetylene	HC≡CCHCH$_2$CH$_2$CHC≡CH (<1)	—	None	105	6	123

Divinylacetylene

Divinylacetylene	CH₂·CH—C(CH=CH₂) (<1) — CH₂—CH=CH—CH₃	(—)	None	81–82	5	14
Ketene diethyl acetal						
Benzalacetophenone	C₆H₅CH—CHCOC₆H₅ (?) (78) — CH₂—C(OC₂H₅)₂	1.6	None	Reflux	12	90
Dibenzalacetone	C₆H₅CH—CHCOCH=CHC₆H₅ (?) (87) — CH₂—C(OC₂H₅)₂	1.4	None	Reflux	12	90
Acrylonitrile		(—)	None	125–300	1–24	25
Methacrylonitrile	NOCHC₆H₅CH₂CHCN (3–7) (cis and trans)	(—)	n-Butyl acetate	240	40	128
Methacrylonitrile	CH₂C(CN)CH₂C₆C(CN)CH₃	(—)	—	200	12	128
α-Methylmercaptoacrylonitrile						
α-Methylmercaptoacrylonitrile	CH₂·C(CN)CH₂C(CH₃)(C(CN))SCH₃ (65) (65)	(—)	None	Room	48	48

Note: References 99 to 127 are on p. 59.
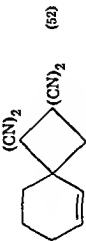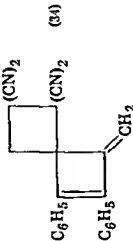
* The yield is based on the addend used in smaller molal amount.

† This is the ratio of the first-named added to the second.

‡ Autogenous pressure is to be understood.

TABLE IV—*Continued*

CYCLOBUTANES FROM THERMAL CYCLOADDITION REACTIONS OF ACTIVATED ALKENES

Addends	Product (Yield, %)*	Mole Ratio†	Solvent	Temp., °C‡	Time, Hours	Refs.
Tetracyanoethylene						
3-Methylenecyclohexene	(52)	1.4	Benzene	Room	12	92
1,2-Dimethylene-3,4-diphenylcyclobutene	(34)	1.8	Benzene	Room	12	92
1,5-Cycloöctadiene						
1,5-Cycloöctadiene	(–)	—	None	Room	190	6
Styrene						
Styrene	$C_6H_5CHCH_2CH_2CH_2CHC_6H_5$ (<5)	—	None, I_2 added	150	24	91
1,1-Diphenylethylene						
1,1-Diphenylethylene	$(C_6H_5)_2CCH_2CH_2C(C_6H_5)_2$ (?) (2–4)	—	$(CH_3O)_2SO_2$	50–55	2–5	93
α-Benzylmercaptoacrylonitrile						
α-Benzylmercaptoacrylonitrile	(50)	—	None	Room	380	48, 124

Author					
Maleic anhydride	p-CH$_3$OOCH.CH=CHCH$_3$ CH=CH (P)	—	—	—	125
Protoanemonin		—	None	Room	—
Protoanemonin		—	None	Room	126, 127

Note. References 99 to 127 are on p. 58.

* The yield is based on the addend used in smaller molal amount.
† This is the ratio of the first-named addend to the second.
‡ Autogenous pressure is to be understood.

CHAPTER 2

THE PREPARATION OF OLEFINS BY THE
PYROLYSIS OF XANTHATES. THE CHUGAEV REACTION*

Harold R. Nace

Brown University

CONTENTS

* Although there are several spellings of Chugaev, the two most common are Tschugaeff and Chugaev. The latter was chosen for this chapter because of its simplicity.

INTRODUCTION

In this chapter the Chugaev reaction is defined as the thermal decomposition of the xanthate ester of an alcohol that contains at least one β-hydrogen atom, to produce one or more olefins, carbon oxysulfide, and a mercaptan.
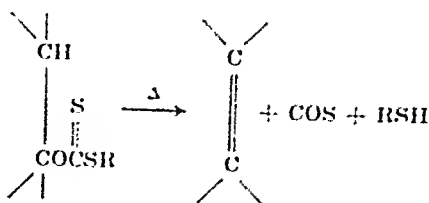
The formation of olefins by the pyrolysis of xanthates was discovered in 1899 by Chugaev[1] in connection with his studies on the optical properties of xanthates[2] and other compounds.[3] He subsequently employed the reaction in his investigations of terpenes and demonstrated both its utility as an olefin-forming reaction and its usefulness in structural determinations.

The reaction, which is particularly valuable for the conversion of sensitive alcohols to the corresponding olefins without rearrangement of the carbon skeleton,[4,5] is analogous to the thermal decomposition of carboxylic esters of alcohols,[6] and of other related derivatives of alcohols, such as carbamates and carbonates,[7] to yield olefins.

MECHANISM[8]

Considerable evidence indicates that the Chugaev reaction proceeds by the formation of a cyclic transition state involving a *cis*-β-hydrogen atom of the alcohol moiety and the thion sulfur atom of the xanthate.

[1] Chugaev, *Ber.*, **32**, 3332 (1899).

[2] Chugaev, *Ber.*, **31**, 1775 (1898).

[3] Lowry, *J. Chem. Soc.*, **123**, 956 (1923).

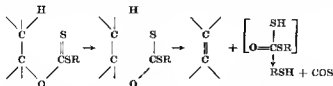[4] Fomin and Sochanski, *Ber.*, **46**, 244 (1913).

[5] Stevens, *J. Am. Chem. Soc.*, **54**, 3732 (1932).

[6] Hurd and Blunck, *J. Am. Chem. Soc.*, **60**, 2419 (1938).

[7] O'Connor and Nace, *J. Am. Chem. Soc.*, **75**, 2118 (1953).

[8] D. J. Cram in Newman, *Steric Effects in Organic Chemistry*, John Wiley & Sons, New York, 1956, Chap. 6. This reference gives a detailed discussion of the mechanism of olefin-forming elimination reactions and defines the term "*cis* elimination" as one in which the leaving groups are departing from the same side of the incipient double bond. In the present discussion, *cis* elimination is used in the sense just defined. In alicyclic compounds of eight and less ring atoms, *cis* elimination requires that the β-hydrogen atom also be *cis* to the xanthate group. Pyrolytic eliminations are also discussed in detail by DuPuy and King, *Chem. Revs.*, **60**, 431 (1960).

Subsequent decomposition, with simultaneous further bond making and breaking, gives the olefin and an unstable dithiocarbonate derivative which subsequently decomposes to carbon oxysulfide and a mercaptan.

$$
\begin{array}{ccc}
\text{H} & \text{H} & \text{SH} \\
\mid & \mid & \mid \\
\text{C} \quad \text{S} & \text{C} \quad \text{S} & \text{O} = \text{CSR} \\
\mid \quad \| & \mid \quad \| & \\
\text{C} \quad \text{CSR} & \text{C} \quad \text{CSR} & \\
& & \text{RSH} + \text{COS}
\end{array}
$$

Huckel, Tappe, and Legutke[*] appear to have been the first to note that the reaction involved a *cis*-β-hydrogen atom, although Hurd and Blunck[*] had made a similar observation earlier with regard to carboxylic esters. Huckel, Tappe, and Legutke postulated a concerted reaction in which the thiol sulfur atom, rather than the thion sulfur atom, attacked and removed the *cis*-β-hydrogen atom.

This suggestion was modified by Barton[10] and by Cram,[11] who proposed that the reaction was completely concerted, involved a *cis*-β-hydrogen atom in alicyclic compounds, and required that the more nucleophilic and less hindered thion sulfur atom attack the β-hydrogen atom. Evidence that the thion sulfur atom, rather than the thiol sulfur atom, attacked the β-hydrogen atom was obtained by Bader and Bourns[12] who made a study of sulfur and carbon isotope effects for the pyrolysis of *trans*-2-methyl-1-indanyl xanthate of natural isotopic abundance. Predicted isotope effects for the thiol sulfur, thion sulfur, and carbonyl carbon were obtained by use of the Bigeleisen equation.[12] As shown in Table I, the observed isotope effect agreed with the one predicted for the mechanism involving the thion sulfur atom.

Cram, in his work on the methyl xanthates of the 3-phenyl-2-butanols[11] and 1,2-diphenyl-1-propanols,[13] also demonstrated that for acyclic compounds the same concerted reaction took place with a high stereospecificity, and that application of the principle of asymmetric induction led to the prediction of the configuration of the olefin.

Barton[10] proposed the term "molecular mechanism" for reactions such as the Chugaev reaction, carboxylic ester pyrolyses, and others, which proceed through a cyclic transition state involving neither ions nor radicals, but rather a redistribution of the electrons accompanied by bond

[*] Huckel, Tappe, and Legutke, *Ann.*, **543**, 191 (1940).
[10] Barton, *J. Chem. Soc.*, **1949**, 2174.
[11] Cram, *J. Am. Chem. Soc.*, **71**, 3883 (1949).
[12] Bader and Bourns, *Can. J. Chem.*, **39**, 348 (1961).
[13] Cram and Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

making and breaking. He also correlated and predicted the configurations of a number of terpenes and other bicyclic compounds, using as a basis the preferred *cis* course of the Chugaev reaction.

TABLE I

Isotope Effects in the Pyrolysis at 80° of S-Methyl *trans*-2-Methyl-1-indanyl Xanthate

| | Per Cent Isotope Effect, $100(k^L/k^H - 1)$[a] | | |
	Thiol Sulfur S^{32}/S^{34}	Thion Sulfur S^{32}/S^{34}	Carbonyl Carbon C^{12}/C^{13}
Predicted			
Thiol sulfur	∼1.2	∼0.0	3.0–4.0
Thion sulfur	∼0.0	0.7–1.0	∼0.0
Found	0.21 ± 0.07	0.86 ± 0.16	0.04 ± 0.06

[a] k^L/k^H is the ratio of the pyrolysis rate constants for the light and heavy isotopes.

Alexander and Mudrak[14-16] provided further convincing evidence for the *cis* elimination course. The methyl xanthates of *cis-* and *trans-*2-phenylcyclohexanol gave phenylcyclohexenes corresponding to *cis* elimination.[14] The methyl xanthate of *cis-*2-methyl-1-tetralol, which has no *cis-β*-hydrogen atom, was stable to pyrolysis, whereas the *trans* isomer readily underwent pyrolysis to give 3,4-dihydro-2-methylnaphthalene.[15] Similar results were obtained with the methyl xanthates of the *cis-* and *trans-*2-methyl-1-indanols.[16]

The concerted *cis* elimination mechanism of the Chugaev reaction requires that it be unimolecular and exhibit first-order kinetics. Evidence that this is so was provided by a kinetic study of the pyrolysis of a number of xanthates of 3β-cholestanol and cholesterol.[7, 17] All the compounds studied showed first-order kinetics for the pyrolysis reaction, and neither the rate nor the order of the reaction was affected by the addition of glass wool, a 2- and 3-cholestene mixture, or radical chain inhibitors such as hydroquinone, diphenylamine, and picric acid. Negative entropies of activation were obtained—an indication that the transition state was highly ordered, as would be expected of a concerted cyclic process.

Several details of the mechanism, however, still require further study. A number of xanthate pyrolyses have been reported in which significant amounts of *trans* elimination were observed. Included among the
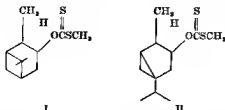
[14] Alexander and Mudrak, *J. Am. Chem. Soc.*, **72**, 1810 (1950).

[15] Alexander and Mudrak, *J. Am. Chem. Soc.*, **72**, 3194 (1950).

[16] Alexander and Mudrak, *J. Am. Chem. Soc.*, **73**, 59 (1951).

[17] O'Connor and Nace, *J. Am. Chem. Soc.*, **74**, 5454 (1952).

examples are the methyl xanthates of the α-decalols,[9] pinocampheol (I)[18] and neothujol (II)[18-22]
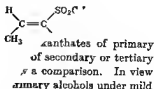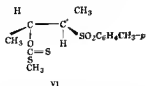

I

II

It is perhaps significant that all the xanthates that underwent *trans* elimination were liquids that could not be purified by distillation. Thus it is possible that some isomerization of the alkoxide ion occurred before the addition of carbon disulfide, and that the apparent *trans* elimination products actually arose from the presence of an isomeric xanthate.

Several unambiguous examples of *trans* elimination in xanthate pyrolyses have been reported by Bordwell and Landis.[23,24] The methyl xanthate (III) of *cis*-2-p-toluenesulfonylcyclohexanol gave the *trans* elimination product, 1-p-toluenesulfonyl-1-cyclohexene (IV) in 40% yield, and little or none of the *cis* product, 3-p-toluenesulfonyl-1-cyclohexene (V).[23]

III

IV

V
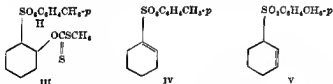
The methyl xanthate (VI) of (±) *erythro*-3-p-toluenesulfonyl-butanol gave *cis*-2-p-toluenesulfonyl-2-butene (VII), the *trans* elim' product, in 38% yield[24]

VI

xanthates of primary of secondary or tertiary s a comparison. In view rimary alcohols under mild

[18] Chugaev, J Russ Phys Chem Soc, 29, 1324 (190)—anthates of primary alcohols
[19] Kondakov and Skworzov, J prakt Chem, (2) 69 m why xanthates of primary
[20] Short and Read, J Chem Soc, 1938, 2016.   f more highly substituted ones.
[21] Chugaev, Ber, 33, 3118 (1900)
[22] Chugaev, Ber, 34, 2276 (1901)
[23] Bordwell and Landis, J Am Chem Soc, 80   [24 (1938) [C A, 23, 2337 (1934)]
[24] Bordwell and Landis J Am Chem Soc, 86

Bordwell and Landis presented evidence that these eliminations proceed by initial ionization of the β-hydrogen atom, rendered more labile by the sulfonyl group on the same carbon atom, to give a dipolar ion intermediate. This intermediate then rearranges to the sterically more favored conformation before decomposing to give the olefin. In each of the cases above, the isomeric *trans*- or *threo*-xanthate gave the same olefin. The effect of other labilizing groups on the β-hydrogen atom has not been investigated.

SCOPE AND LIMITATIONS

Olefin-forming xanthates have been prepared (and pyrolyzed) from primary alcohols, secondary acyclic and alicyclic alcohols, tertiary acyclic and alicyclic alcohols, glycols, and dihaloalkanes. The S-methyl xanthates have been most frequently employed, but higher S-alkyl and S-benzyl and substituted S-benzyl xanthates have also been used.

Xanthates of Primary Alcohols

Pyrolyses of xanthates of primary alcohols are surprisingly few in number. *n*-Amyl S-methyl xanthate gave 1-pentene (15%), and isoamyl S-methyl xanthate gave isopropylethylene (15%).[25] It was stated that these yields were minimal and could probably be doubled by more careful isolation of the olefins.

The methyl xanthate (VIII) of neopentyl alcohol, which has no β-hydrogen atom, rearranged on pyrolysis to give the more stable dithio-thiobonate IX in 70% yield.[26]

of xan.
studied sh.
the rate nor
wool, a 2- and

$$(CH_3)_3CCH_2OCSCH_3 \quad\quad (CH_3)_3CCH_2SCSCH_3$$
$$\overset{\text{S}}{\|} \qquad\qquad\qquad\qquad \overset{\text{O}}{\|}$$

hydroquinone, diph VIII IX
activation were obtai.
highly ordered, as would thate (X), which also has no β-hydrogen atom
Several details of the in, on pyrolysis at 160–185° gave stilbene
A number of xanthate pyr (%),[27] and the dithiocarbonate XI.[27] The
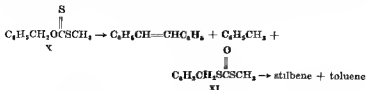amounts of *trans* elimina is at 290° gave stilbene (60%) and toluene
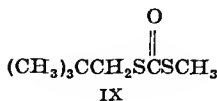
14 Alexander and Mudrak, *J. Am. Chem. Soc.*, **55**, 3809 (1933).
15 Alexander and Mudrak, *J. Am.* ?, 8 (1940) [*C.A.*, **34**, 5059 (1940)].
16 Alexander and Mudrak, *J. Am.* ?, 19 (1943) [*C.A.*, **40**, 4687 (1946)].
17 O'Connor and Nace, *J. Am. Chem. Chem.*, (2) 112, 164 (1926).

(25%). Although these pyrolyses appear to involve free-radical intermediates, little direct evidence with respect to the mechanism is available.

$$C_4H_5CH_2OCSCH_3 \rightarrow C_6H_4CH{=}CHC_4H_9 + C_4H_5CH_3 +$$

$$\overset{\text{S}}{\underset{\text{X}}{\text{ }}}$$

$$\overset{\text{O}}{C_6H_4CH_2SCSCH_3} \rightarrow \text{stilbene} + \text{toluene}$$

$$\text{XI}$$

The methyl xanthates of cyclohexylcarbinol and 4-methylcyclohexyl-carbinol were pyrolyzed to give, in unstated yield, methylenecyclohexane and methylene-4-methylcyclohexane,[29] respectively.

The methyl xanthate (XII) of diacetone galactose underwent pyrolysis on heating, but the unidentified product was not an olefin.[30]

XII
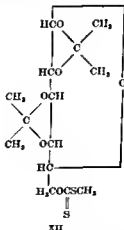
Although the statement has been made that xanthates of primary alcohols are more stable to pyrolysis than those of secondary or tertiary alcohols,[25] there is not enough evidence to allow a comparison. In view of the lack of good methods for dehydrating primary alcohols under mild conditions, further study of the pyrolysis of xanthates of primary alcohols seems desirable. There is no obvious reason why xanthates of primary alcohols should be more stable than those of more highly substituted ones.

29 Alexandrovitsch, J. Gen. Chem. (U.S.S.R.), 3, 48 (1933) [C. A., 28, 2337 (1934)]

30 Freudenberg and Wolf, Ber., 60, 232 (1927)

Xanthates of Secondary Alcohols

The Chugaev reaction has been widely employed for the conversion of both acyclic and alicyclic secondary alcohols to olefins.

Acyclic Alcohols. Depending on the degree of substitution on the carbon atoms adjacent to the carbinol carbon atom of acyclic alcohols, elimination may proceed in more than one direction to give structural isomers. These in turn may be mixtures of *cis* and *trans* forms. Where elimination is possible in only one direction, the olefin may be *cis* or *trans*, again depending on the degree of substitution.

The configuration of the olefin is determined, in part, by the stereochemistry of the xanthate. In acyclic compounds the β-hydrogen atom and the xanthate group must be coplanar in the transition state, and this requirement in turn determines the configuration of the olefin. If more than one β-hydrogen atom is present, both the *cis* and the *trans* isomer may result, the proportion being partially dependent on the size of the other substituents on the two incipient olefin carbon atoms. When the steric factor is not dominant, the thermodynamically more stable *trans* olefin will predominate.

At least three factors determine the direction of elimination in xanthate pyrolysis (and ester pyrolyses in general): (1) the statistical, whereby the carbon atom carrying the greatest number of hydrogen atoms provides more chances for formation of the cyclic transition state; (2) the thermodynamic, whereby the more stable of the various possible olefins is preferred (the stability depending on the degree of "olefin-character" in the transition state), and (3) the steric, which affects the energies of the various possible transition states.

In many Chugaev reactions involving acyclic secondary alcohols, it is difficult to determine which of these three factors is dominant, and frequently one factor is excluded or is opposed by the other two. However, an understanding of them is useful in predicting the outcome of the Chugaev reaction.

The pyrolyses of the S-methyl xanthates of *erythro-* and *threo-*1,2-diphenyl-1-propanol, where elimination in only one direction is possible, afford an interesting example of the effect of steric factors on the ease of decomposition of the xanthate and provide good evidence that the Chugaev reaction proceeds by a *cis* elimination with acyclic compounds.[13]

In the cyclic transition state (XIII) for the S-methyl xanthate of *erythro-*1,2-diphenyl-1-propanol, the phenyl groups are on opposite sides of the incipient double bond; the only olefin isolated was *trans-α-*methylstilbene (XIV, 77%).[13]
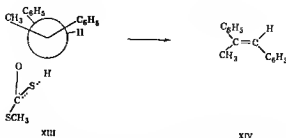
Conversely, in the transition state (XV) for the *threo*-xanthate, the phenyl groups are on the same side of the incipient double bond; the only olefin isolated was *cis*-α-methylstilbene (XVI, 65%).[13]
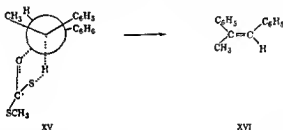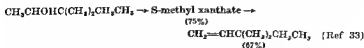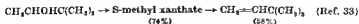

Decomposition of the *erythro*-xanthate began at 130°, and of the *threo*- at 145°, showing that the interference between the two phenyl groups increased the activation energy of the latter pyrolysis.

The pyrolysis of the methyl xanthate of diethylcarbinol gave *trans*-2-pentene in 55% yield (alkyl groups on an opposite sides of the incipient double bond in the transition state) and *cis*-2-pentene in 33% yield[31] (alkyl groups on the same side), further illustrating the steric effects.

The methyl xanthate of di-undecylcarbinol gave 11-tricosene; the yield and configuration were not stated[32]
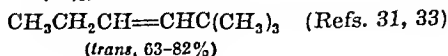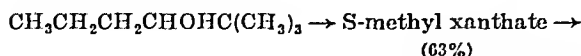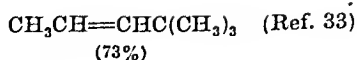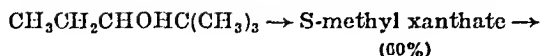
The utility of the Chugaev reaction for the formation of olefins without rearrangement of the carbon skeleton is shown by the following examples.

$$CH_3CHOHC(CH_3)_3 \rightarrow S\text{-methyl xanthate} \rightarrow CH_2=CHC(CH_3)_3 \quad \text{(Ref. 33)}$$
$$\text{(74%)} \qquad\qquad\qquad\qquad\qquad\qquad \text{(58%)}$$

$$CH_3CHOHC(CH_3)_2CH_2CH_3 \rightarrow S\text{-methyl xanthate} \rightarrow$$
$$\text{(75%)}$$
$$CH_2=CHC(CH_3)_2CH_2CH_3 \quad \text{(Ref. 33)}$$
$$\text{(57%)}$$

[31] Bonkeuer, Herzira and Barrous, *J Am Chem Soc*, **61**, 5374 (1929).
[32] Petrov, Karassew, and Tscholzows, *Bull soc chim France*, (5) **3**, 174 (1936).
[33] Schurman and Boord, *J Am Chem Soc*, **55**, 4930 (1933)

$CH_3CH_2CHOHC(CH_3)_3 \rightarrow$ S-methyl xanthate $\rightarrow$
(60%)

$$CH_3CH=CHC(CH_3)_3 \quad \text{(Ref. 33)}$$
(73%)

$CH_3CH_2CH_2CHOHC(CH_3)_3 \rightarrow$ S-methyl xanthate $\rightarrow$
(63%)

$$CH_3CH_2CH=CHC(CH_3)_3 \quad \text{(Refs. 31, 33)}$$
(trans, 63-82%)

$CH_3CH_2CHOHC(CH_3)_2CH_2CH_3 \rightarrow$ S-methyl xanthate $\rightarrow$
(41%)

$$CH_3CH=CHC(CH_3)_2CH_2CH_3 \quad \text{(Ref. 33)}$$
(55%)
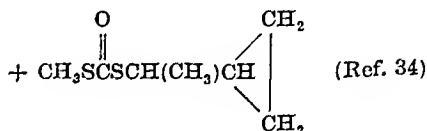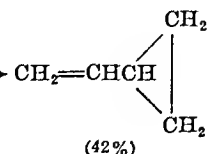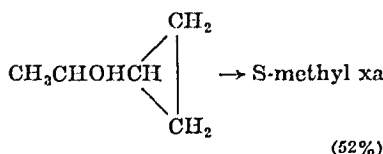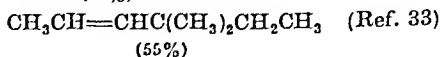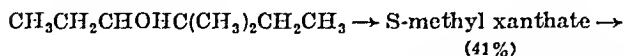
Each of these alcohols is of the type which on non-pyrolytic dehydration gives rearranged olefins.[35] Thus methylcyclopropylcarbinol on dehydration with sulfuric acid gave vinylcyclopropane (8%), 1,4-pentadiene (0.4%), cyclopentene (0.9%), and 2-methyltetrahydrofuran (10%). The acetate of the same carbinol, in contrast to the xanthate, gave vinylcyclopropane (10%), cyclopentene (60%), 1,4-pentadiene (9%), and trace amounts of isoprene and trans-1,3-pentadiene.[34]

In three of the olefins above, cis-trans isomerism is possible, but only in the case of trans-2,2-dimethyl-3-hexene was the configuration determined. The bulk of the t-butyl and ethyl groups is apparently too large to permit the formation of the cis olefin. Presumably 2,2-dimethyl-3-pentene and 3,3-dimethyl-4-hexene also have the trans configuration for the same reason.

When elimination in more than one direction is possible, and more than one β-hydrogen atom is available on each carbon atom, the synthetic utility of the Chugaev reaction is greatly diminished by the formation of complex mixtures of olefins.

[34] Overberger and Borchert, J. Am. Chem. Soc., 82, 4896 (1960).
[35] Wagner and Zook, Synthetic Organic Chemistry, p. 32. John Wiley & Sons, New York, 1953.

The S-methyl xanthate (25% yield) of 3-hexanol gave *trans*-3-hexene (28%), *cis*-3-hexene (13%), *trans*-2-hexene (29%), and *cis*-2-hexene (13%)[31] Similarly, the S-methyl xanthate (30% yield) of ethylisobutylcarbinol gave *trans*-2-methyl-3-hexene (43%), *cis*-2-methyl-3-hexene (5%), *trans*-2-methyl-4-hexene (28%), and *cis*-2-methyl-4-hexene (9%).[31] As expected, the direction of elimination in these examples conforms to statistical prediction, and the *trans* isomer predominates over the *cis*.

When the S-methyl xanthate of ethylneopentylcarbinol is pyrolyzed, a strong preference for elimination toward the bulky alkyl group is evidenced Thus 2,2-dimethyl-3-hexene (58% *trans*, 2% *cis*) is formed in 60% yield and 2,2-dimethyl-4-hexene (21% *trans*, 5% *cis*) is formed in only 26% yield [31] The explanation advanced for this behavior is that, when the xanthate moves into the transition state (XVII) for elimination toward the bulky alkyl group, some steric assistance is provided by the separation of the ester and *t*-butyl groups, or the ethyl and *t*-butyl groups, and this steric assistance is not provided when elimination proceeds in the other direction (XVIII).[31]
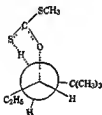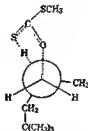

XVII   XVIII

The pyrolysis of S-methyl *sec*-octyl xanthate gave a mixture of 2-octene (21–23%) and 1-octene (23–25%)[33] Although the terminal olefin is less stable, it is favored statistically because there are three hydrogen atoms available for elimination in this direction, compared to two in the other
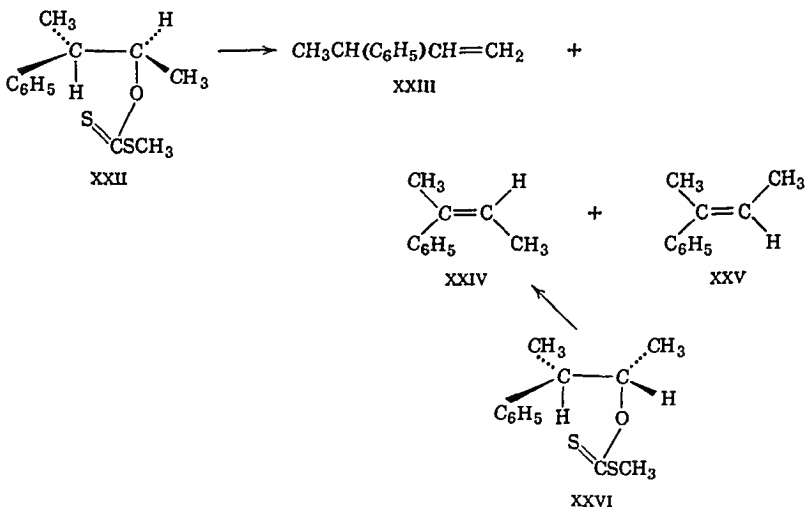
The S-methyl xanthate (XIX, 57% yield) of methylcyclohexylcarbinol gave a mixture consisting of cyclohexylethylene (XX, 32%), and ethylidenecyclohexane (XXI, 20%)[36] Although the statistical factor favors the formation of cyclohexylethylene, no information about the relative stabilities of the two olefins is available.

The pyrolysis of the xanthates of *erythro*- and *threo*-3-phenyl-2-butanol[11] illustrates the difficulty of assessing all three of the factors (statistical,

[33] Benkeser and Hazdra, *J Am Chem Soc*, **81**, 228 (1959),

S
‖
$CH_3CHOCSCH_3$

$\xrightarrow{250°}$

CH_2
‖
CH

+

$CHCH_3$

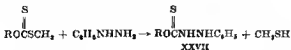XIX   XX   XXI
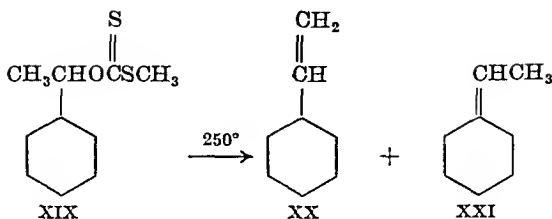
thermodynamic, and steric) involved in predicting the course of elimination. The S-methyl xanthate (XXII) of *erythro*-3-phenyl-2-butanol gave 2-phenyl-3-butene (XXIII, 32%), *trans*-2-phenyl-2-butene (XXIV, 45%), and *cis*-2-phenyl-2-butene (XXV, 5%).[11]

CH_3 H

C—C

C_6H_5 H CH_3

S   O

$CSCH_3$

XXII

$\longrightarrow$ $CH_3CH(C_6H_5)CH{=}CH_2$ +

XXIII

CH_3 H

$C{=}C$

C_6H_5 CH_3

XXIV

+

CH_3 CH_3

$C{=}C$

C_6H_5 H

XXV

CH_3 CH_3

C—C

C_6H_5 H   O   H

S

$CSCH_3$

XXVI

The yields of olefins from the corresponding *threo*-xanthate XXVI were 36% of the *cis* olefin XXV, 11% of the *trans* olefin XXIV, and 37% of the terminal olefin XXIII. For each xanthate, the statistical factor favors terminal olefin, the thermodynamic factor favors internal olefin, and it is difficult to evaluate the steric factors.

The isolation of *cis* olefin (5%) from the *erythro*-xanthate and *trans* olefin (11%) from the *threo*-xanthate appears to indicate a *trans* elimination path for the Chugaev reaction. However, several other explanations may be suggested. The pyrolysis could have proceeded by an inter-, rather than an intra-molecular path.[11] Little or no evidence is available to indicate whether such a route is available for pyrolytic eliminations, however.

A second explanation lies in the fact that the xanthates were liquids, purified by distillation, and each may not have been free of the other isomer. In the first step in the preparation of the xanthates the corresponding alcohol was heated under reflux with potassium metal. It is well known that metal alkoxides can undergo epimerization under these conditions [37] The presence of a small amount of the isomeric xanthate would be difficult to detect, although its presence might be shown by conversion to the corresponding phenylhydrazine derivative (XXVII), [38] followed by fractional crystallization or chromatography.

$$
\begin{array}{ccc}
\text{S} & & \text{S} \\
\| & & \| \\
\text{ROCSCH}_3 + \text{C}_6\text{H}_5\text{NHNH}_2 & \rightarrow & \text{ROCNHNHC}_6\text{H}_5 + \text{CH}_3\text{SH} \\
& & \text{XXVII}
\end{array}
$$

It is also possible that a portion of the xanthate decomposes by a reaction path involving the formation of the dipolar ion type of intermediate, [34] discussed previously, which leads to olefins by a route quite different from the concerted Chugaev reaction.

Finally, a portion of the xanthate decomposition may be peroxide induced, again following a different path, as discussed below for the case of (−)-menthyl S-methyl xanthate Other examples of apparent *trans* Chugaev decompositions will be noted, and the same possible explanations may be applied Further study is obviously necessary to determine the correct explanation

Similar results were obtained with the S-methyl xanthate of erythro-2-phenyl-3-pentanol, which gave 2-phenyl-3-hexene (37%), *trans*-2-phenyl-2-hexene (27%), and cis-2-phenyl-2-hexene (4%), the last compound corresponding to a *trans* Chugaev elimination. [11]

Alicyclic Alcohols. In the pyrolysis of the xanthates of alicyclic secondary alcohols, an additional restriction on the stereochemistry is imposed if the Chugaev reaction is to proceed by the cis elimination path. Coplanarity of the β-hydrogen atom and the xanthate group is required in the cyclic transition state, and, in order to avoid high energies due to bond and ring distortion, the groups must be cis to each other. For six-membered rings, this requires that one group be axial and the other equatorial It has been pointed out [39] that theoretically the two groups can be *trans* and diequatorial, but that considerable ring distortion is required for coplanarity in the transition state This high energy

[37] Doering and Aschner, *J Am Chem Soc*, **71**, 838 (1949)
[38] Balmer and Mann, *J Chem Soc*, **1945**, 666
[39] Dauben and Pitzer, in Newman, *Steric Effects in Organic Chemistry*, p 49, John Wiley & Sons, New York, 1958

requirement makes *trans* elimination unlikely under the usual conditions
of the Chugaev reaction.

The reaction thus becomes a useful method for determining the con-
figuration of cyclic *β*-substituted alcohols, since the relationship of the
hydroxyl and substituent is readily ascertainable by observation of the
direction of elimination of the xanthate.   The steric course also has
synthetic applications, since the position of the double bond to be intro-
duced can be controlled by choosing the appropriate isomer for pyrolysis.

In the one reported example of the pyrolysis of a cyclobutyl xanthate,
ring cleavage occurred.   Cyclobutyl S-methyl xanthate (XXVIII, 84%
yield) was pyrolyzed at 255° to give 1,3-butadiene in quantitative yield.[40]
The reaction was pictured[40] as involving the simultaneous redistribution
of electrons and bond making and breaking, as shown for XXVIII.
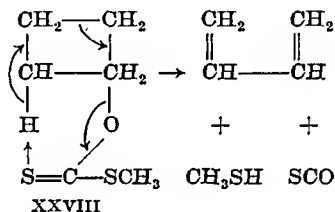
Several examples involving five-membered rings have been reported.
The S-methyl xanthate (90% yield) of cyclopentanol at 255° gave cyclo-
pentene in 70% yield.[40]

Pyrolysis of the S-methyl xanthate (XXIX) of *trans*-1-hydroxy-2-
methylindane at 98–100° gave 2-methylindene (XXX) in 80% yield.[16]
When the corresponding *cis*-xanthate (XXXI) was pyrolyzed at the same
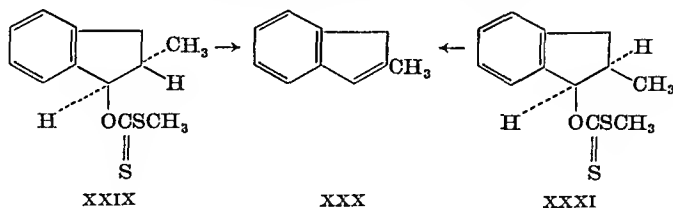
temperature, the yield of 2-methylindene was only 20%, regardless of the
pyrolysis time,[16] suggesting the presence of an impurity in the xanthate.
At higher temperatures, more deep-seated decomposition was observed,
with no increase in yield of 2-methylindene.

[40] Roberts and Sauer, *J. Am. Chem. Soc.*, **71**, 3925 (1949).

No such complications were encountered in the pyrolyses of the homologous tetralyl isomers.[15] *trans*-S-Methyl 2-methyl-1-tetralyl xanthate (XXXII) pyrolyzed readily at 98–100° to 2-methyl-3,4-dihydronaphthalene (XXXIII), while the *cis* isomer (XXXIV) was inert.
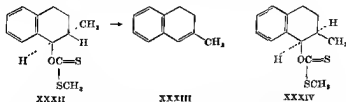
In general, xanthates derived from substituted cyclohexanols undergo the Chugaev reaction in the expected manner at temperatures in the range 100–250°, as shown by the following examples
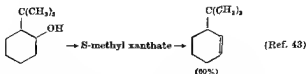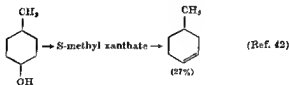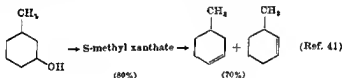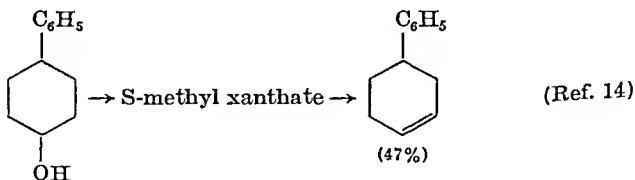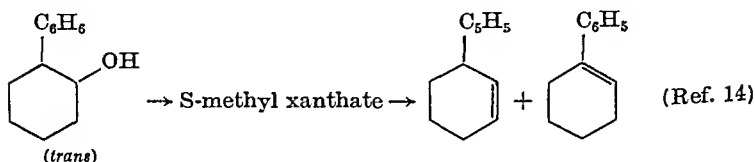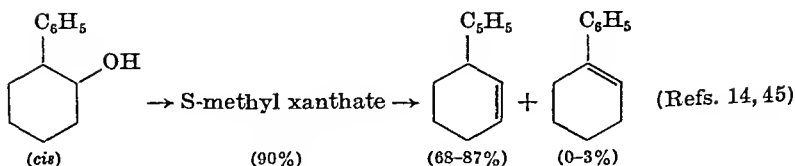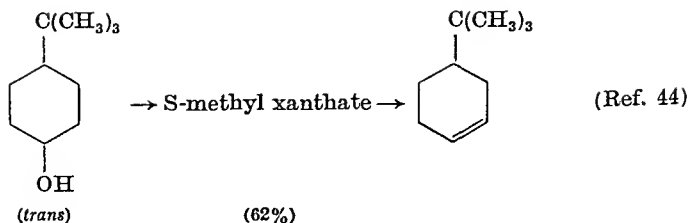
41 Mackownkov and Stadnikov, *J Russ Phys Chem Soc*, **35**, 382 (1903) [*Chem Zentr*, 1903, II, 2891; *Ann*, **336**, 310 (1904)
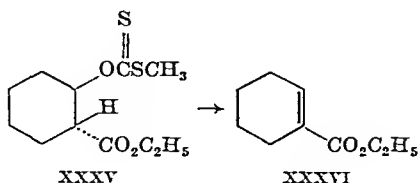42 Nametkin and Brussov, *Ber*, **55**, 1807 (1923)
43 Bordwell and Landis, *J Am Chem Soc*, **80**, 6379 (1958).

A few examples with substituents other than alkyl or aryl have been reported. The S-methyl xanthate (XXXV) of ethyl *trans*-cyclohexanol-2-carboxylate gave only ethyl 1-cyclohexenecarboxylate (XXXVI) in 34% yield.[46]

[44] Winstein and Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

[45] Berti, *J. Am. Chem. Soc.*, **76**, 1216 (1954).

[46] Mousseron and Canet, *Compt. rend.*, **233**, 525 (1951); *Bull. soc. chim. France*, **1952**, 190.

cis-2-*p*-Tolylthiocyclohexyl S-methyl xanthate (XXXVII) gave 3-*p*-tolylthio-1-cyclohexene (XXXVIII, 49–51%) accompanied by as much as 5–10% of the *trans* elimination product, 1-*p*-tolylthio-1-cyclohexene (XXXIX).[23] The isomeric *trans*-xanthate (XL) gave 1-*p*-tolylthio-1-cyclohexene (XXXIX, 85% yield).[23]
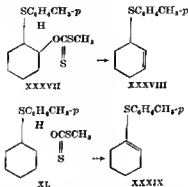
When the corresponding sulfones were pyrolyzed, the reaction appeared to follow a different course. *trans*-2-*p*-Tolylsulfonylcyclohexyl S-methyl xanthate (XLI) gave 1-*p*-tolylsulfonyl-1-cyclohexene (XLII, 77%), corresponding to *cis* elimination. However, the *cis* isomer XLIII gave almost exclusively the same olefin in 40% yield, corresponding to a *trans* elimination.[23]
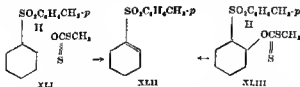

As in the case of the analogous acyclic sulfonyl-substituted compounds referred to earlier, the hypothesis has been advanced that the pyrolysis involves the formation of a dipolar ion XLIV, which decomposes to the

olefin.[23]   This stepwise decomposition is believed to be energetically more favorable than a concerted one because of the increased acidity of the β-hydrogen atom which is adjacent to the sulfonyl group.

The *cis-* and *trans-α-* and *-β-*decalyl S-methyl xanthates have been pyrolyzed at temperatures between 100° and 210° to yield mixtures of olefins.[9, 47]

One example of the pyrolysis of a cycloheptyl xanthate has been reported.   The   S-methyl   xanthate   of   1,1,7-trimethyl-2-hydroxy-3-diethoxymethylcycloheptane (XLV), heated at 200–210° in the presence of copper-bronze, gave in 50% yield an olefin of unknown structure, isomeric with the expected product.[48]

XLV
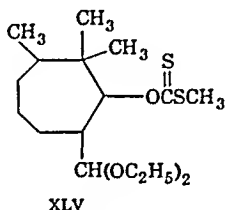
Pyrolysis of the S-methyl xanthates of cyclooctanol[49a] cyclononanol,[49b] and cyclodecanol[49a, c] points out that pyrolytic *cis* eliminations of alicyclic compounds give *cis* olefins only when the carbocyclic ring has eight or fewer carbon atoms.   Thus cyclooctyl S-methyl xanthate when pyrolyzed at 135–290°, gave *cis*-cyclooctene (88%) and no *trans* isomer.[49a]

Cyclononyl S-methyl xanthate gave mixtures of *cis-* and *trans-*cyclononene, and, above 400°, ring cleavage was observed in addition to the

Temp.	% cis	% trans	% diene
120–130°	21	14	0
360°	24	20	0
400°	30	7	Trace
450°	32	8	4.5
500°	12	0	12
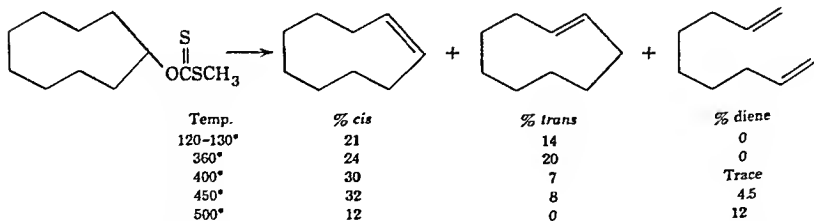
normal elimination.[49b]   Two explanations were proposed for the formation of the 1,8-nonadiene.   One explanation, that the diene is formed by rearrangement of cyclononenes, is supported by studies on the thermal

[47] Hückel and Naab, *Ann.*, 502, 136 (1933).
[48] Ruzicka, Seidel, Schinz, and Pfeiffer, *Helv. Chim. Acta*, 31, 422 (1948).
[49] (a) A. C. Cope and M. Youngquist, to be published. (b) Blomquist and Taussig, *J. Am. Chem. Soc.*, 79, 3505 (1957). (c) Blomquist and Goldstein, *J. Am. Chem. Soc.*, 77, 1001 (1955).

decomposition of mixtures of the two cyclononenes at 500° which show that the *cis* and, especially, the *trans* isomer undergo transannular intramolecular rearrangement to the open-chain diene. The other, that the reaction goes through a six-membered cyclic transition state involving the oxygen atom and a hydrogen on the C-4 carbon atom, is suggested because such a transition state appears quite feasible sterically.[49b] Apparently neither route is energetically as favored as the Chugaev reaction at temperatures below 450°

When cyclodecyl S-methyl xanthate is pyrolyzed (135–220°), the *trans* olefin (38–50%) predominates over the *cis* (6–11%).[49b, c]

The Chugaev reaction has had wide application in the study of both synthetic and structural problems in the terpenoid field. The reaction has been used to determine the configuration of hydroxyl groups, and, conversely, when configuration is known, the position of the double bond introduced by pyrolysis of the xanthate has been inferred on the basis of the preferred *cis* course of the Chugaev reaction.[10]

The availability of gas chromatography and nuclear magnetic resonance should stimulate and facilitate reinvestigation of those examples of the Chugaev reaction with terpenoids where the stereochemistry of the alcohol or olefin or the composition (presence of isomers) of the alcohol or olefin were not known with certainty

Camphenilyl S-methyl xanthate (XLVI) was pyrolyzed to give, in unstated yield, apobornylene (XLVII), with[50] or without[51] the additional product, apocyclene (XLVIII).


XLVI   XLVII   XLVIII
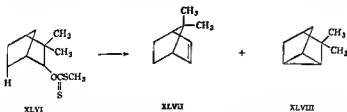
Apobornylene represents a rearrangement product, while the apocyclene indicates elimination of a hydrogen atom from a carbon atom β to the xanthate-bearing carbon atom of the ring. In a sense this hydrogen atom is equivalent to a β-hydrogen atom. It is known that compounds of these types may be in equilibrium at elevated temperatures in the

⁴⁹ Komppa and Roscher, *Ann.* **429, 175** (1922)
⁵¹ Wagner and Lemeschewska, *Beilstein's Handbuch der organischen Chemie*, 4th ed., Vol. 5, p. 123, J. Springer, Berlin, 1922

presence of silica and alumina,[52,53] and thus one of these products may be an artifact rather than a true Chugaev product.

No rearrangement occurred with (−)-bornyl S-methyl xanthate (XLIX), which gave (+)-bornylene (L)[54–56] in yields up to 96%,[56] or (+)-bornylene and tricyclene (LI).[57,58] However, the pyrolysis of

XLIX   L   LI
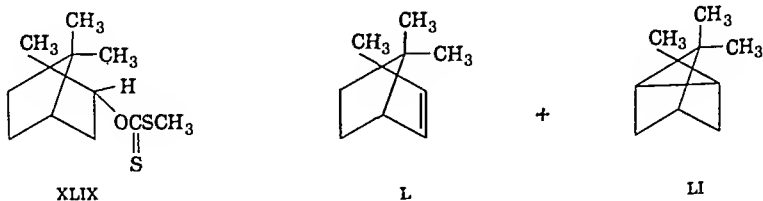
(−)-bornyl dixanthide (LII) gave camphene (LIII)[59] in addition to (+)-bornylene (L) and (−)-borneol (LIV).

LII   LIII   LIV

L
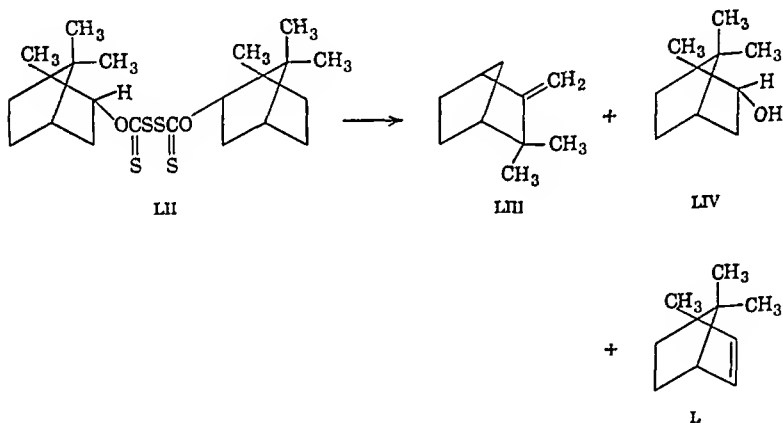
(+)-Bornyl[55] and (−)-epibornyl (LV)[60] S-methyl xanthates gave only (−)-bornylene (L), but isobornyl S-methyl xanthate (LVI) gave only the rearranged product, camphene (LIII),[61] again indicating rearrangement during or after the elimination.

[52] Schleyer, J. Am. Chem. Soc., 80, 1700 (1958).
[53] Swann and Cripwell, Ind. Eng. Chem., 40, 573 (1948).
[54] McAlpine, J. Chem. Soc., 1931, 1114.
[55] Chugaev, J. Russ. Phys. Chem. Soc., 36, 988 (1904) [Chem. Zentr., 1905, I, 93].
[56] Chugaev and Budrick, Ann., 388, 280 (1012).
[57] Henderson and Caw, J. Chem. Soc., 101, 1416 (1912).
[58] Shriner and Sutherland, J. Am. Chem. Soc., 60, 1314 (1938).
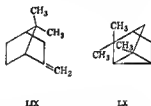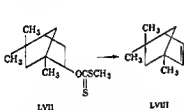[59] McAlpine, J. Chem. Soc., 1932, 912.
[60] Bredt and Perkin, Jr., J. Chem. Soc., 103, 2224 (1013).
[61] Hückel, Ber., 77, 805 (1944).

LV   LVI

Pyrolysis of the S-methyl xanthate (LVII) of α-isofenchyl alcohol gave isofenchylene (LVIII)[42-44] and, in one instance, α-fenchene (LIX) and cyclofenchene (LX)[45]

LVII   LVIII   LIX   LX

The S-methyl xanthate (LXI) of α-fenchyl alcohol should be incapable of undergoing the Chugaev reaction, since there are no hydrogen atoms, cis or trans, on either of the carbon atoms adjacent to the one carrying the xanthate group. However, it has been reported[29, 44-46] to give α-fenchene (LIX) and cyclofenchene (LX) in yields up to 72%[44] for the mixture of olefins. Cyclofenchene results from elimination of a hydrogen atom from a γ-carbon atom, while α-fenchene must arise by rearrangement.

LXI   →   LIX + LX
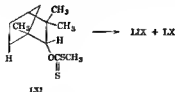
42 Nametkin J prakt Chem, (2) 106, 25 (1923)

43 Nametkin and Rushentzova J Russ Phys Chem Soc, 48, 450 (1916) [C A , 11, 583 (1917)]

44 Qvist, Ann, 417, 278, 285, 307 (1918)

45 Komppa and Nyman, Ann, 535, 252 (1938)

46 Nametkin and Selivanova, J Russ Phys Chem Soc, 49, 417 (1917) [C A , 18, 1486 (1924)]

Several examples from the terpene field further illustrate the stability of three- and four-membered rings at the temperatures necessary for pyrolysis of xanthates. (−)-Caryl S-methyl xanthate (LXII), when heated to its boiling point, gave Δ^4-carene.[67]
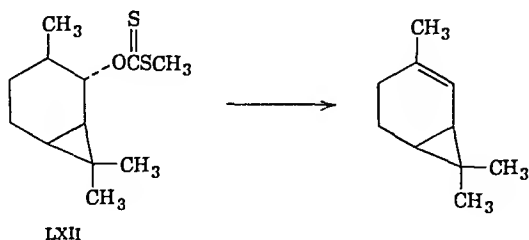
LXII

There are several reports of the pyrolysis, at temperatures up to 190°, of the S-methyl xanthate (LXIII) of thujyl alcohol (of uncertain configuration) to give α-thujene (LXIV), and β-thujene (LXV).[19, 31, 22, 68–70]

LXIII   LXIV   LXV   LXVI
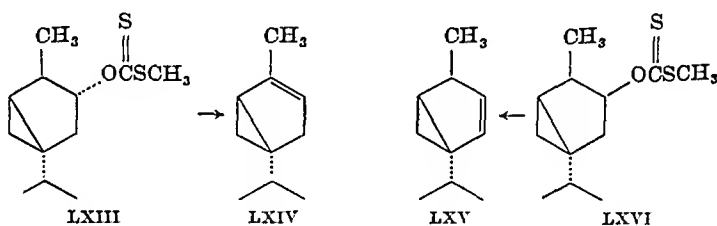
The formation of α-thujene indicates that the xanthate and methyl groups must be *trans* to each other, and this assignment is supported by the fact that the S-methyl xanthate (LXVI) of (−)-neothujyl alcohol gave only β-thujene (LXV).[10, 20]

The S-methyl xanthate (LXVII) of (−)-pinocampheol gave mixtures of δ-pinene (LXVIII) and α-pinene (LXIX),[18, 71] the yields in one experiment being 21 and 17%, respectively.[72] The S-methyl xanthate (LXX) of isopinocampheol gave α-pinene (LXIX) in 38% yield.[72] No other olefins were reported.

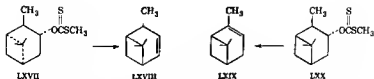[67] Menon and Simonsen, *J. Indian Inst. Sci.*, **10A**, 4 (1927) [*C.A.*, **21**, 3192 (1927)].

[68] Henderson and Robertson, *J. Chem. Soc.*, **123**, 1713 (1923).

[69] Kondakov and Skworzov, *J. Russ. Phys. Chem. Soc.*, **42**, 497 (1910) [*Chem. Zentr.*, 1910, II, 467].
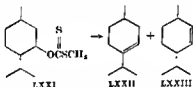
[70] Chugaev and Fomin, *Ber.*, **45**, 1293 (1912).

[71] Gildemeister and Kohler, *Wallach Festschrift*, 414 (1909) [*Chem. Zentr.*, 1909, II, 2158].

[72] Schmidt, *Ber.*, **77**, 544 (1944).

LXVII   LXVIII   LXIX   LXX

The most thoroughly studied terpenoid xanthate is (−)-menthyl S-methyl xanthate (LXXI), which on pyrolysis gives in 51% yield a 3:1 mixture of 3-menthene (LXXII) and 2-menthene (LXXIII).[9, 73]

LXXI   LXXII   LXXIII

The occurrence of an unstable form of the xanthate,[54, 74] which decomposed at lower temperatures than did the normal xanthate, was shown to be due to the presence of peroxidic impurities.[73] An unstable form of the S-methyl xanthate (XLIX) of (−)-borneol was also noted.[74] The cause of the instability has not been established, although it is probably the same as that for the menthyl xanthate. Little is known about the effect of peroxides on xanthate pyrolyses.

The effect of varying the S-alkyl group on the stability of the xanthate toward pyrolysis was shown qualitatively by using (−)-menthyl xanthates.[74] An S-isopropyl group increased the stability relative to an S-methyl group, while an S-benzyl group decreased the stability, and an S-p-nitrobenzyl group decreased it still more, suggesting that electronegative groups on the thiol sulfur decrease the activation energy for the Chugaev reaction. Replacement of the S-methyl portion by an amide group appeared to increase the stability, for temperatures in the range 200–220° were necessary for pyrolysis of the xanthogen amide LXXIV.[75]
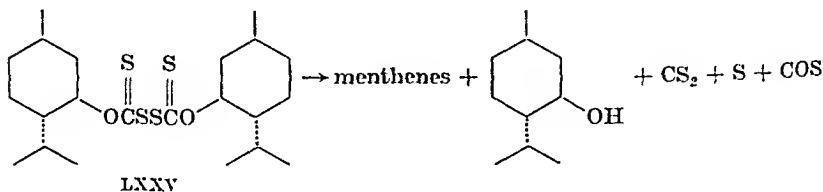

LXXIV   → menthenes + NH₃ + COS

---
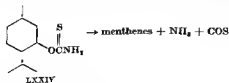
⁹² Nace, Manly, and Fusco, *J. Org. Chem.*, **23**, 687 (1958).
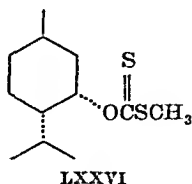
⁷⁴ McAlpine, *J. Chem. Soc.*, **1932**, 906.

⁷⁵ Chugaev, *Ber.*, **35**, 2473 (1902).

The dixanthide LXXV appeared to be less stable than the S-methyl xanthate, but only one of the menthyl groups underwent elimination, the other giving (−)-menthol.[1,59]

LXXV

The S-methyl xanthate (LXXVI) of (+)-neomenthol gave only 2-menthene in 80% yield.[9]

LXXVI

The S-methyl xanthate (LXXVII) of *endo*-5-hydroxybicyclo-[2.2.1]-2-heptene proved difficult to pyrolyze, giving at 250° only a 5% yield of bicyclo-[2.2.1]-2,5-heptadiene.[76] The corresponding acetate and trimethylammonium hydroxide failed completely to undergo pyrolysis at the same temperature.[76]

LXXVII
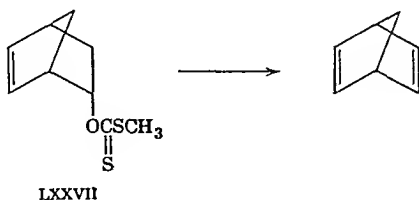
The Chugaev reaction has not been widely employed in the steroid field, but in the cases studied the yields of olefins were generally high. Cholesteryl S-methyl xanthate gave 3,5-cholestadiene in yields up to 93%.[17,77] Good yields (65–90%) were also obtained with a variety of other alkyl groups on the thiol sulfur atom.[7] Rate studies on the

[76] Parham, Hunter, Hanson, and Lahr, *J. Am. Chem. Soc.*, **74**, 5646 (1952).

[77] Eck, Van Peursem, and Hollingsworth, *J. Am. Chem. Soc.*, **61**, 171 (1939).

decomposition of these xanthates showed that an increase in the electro-negativity of the S-alkyl group decreased the stability of the xanthate in the following order [7]

$$C_4H_9 > CH_3 > C_6H_5CH_2 > p\text{-}CH_3OC_6H_4CH_2 > p\text{-}C_6H_5CH_2 >$$
$$(C_6H_5)_2CH > p\text{-}O_2NC_6H_4CH_2 > (C_6H_5)_3C$$
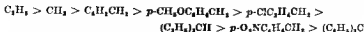
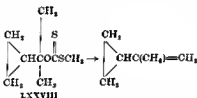In comparison, cholesteryl methyl trithiocarbonate, in which the oxygen atom of the xanthate group has been replaced by sulfur, decomposed even slower than the S-methyl xanthate, to give 3,5-cholestadiene in 80% yield.[7]

Cholestanyl S-methyl and S-benzyl xanthates, on pyrolysis at 230°, gave a 1.1 mixture of 2- and 3-cholestene in yields of 94 and 92%, respectively.[17]

Xanthates of Tertiary Alcohols

The behavior of tertiary alcohols in the Chugaev reaction is comparable to that of primary and secondary alcohols, although very few examples have been reported.

Acyclic Tertiary Alcohols. Xanthates of only four acyclic tertiary alcohols have been pyrolyzed. The S-methyl xanthate (LXXVIII) of dimethylcyclopropylcarbinol was pyrolyzed at 130–135° in xylene to give isopropenylcyclopropane in 24% yield.[76] The S-methyl xanthate of

$$
\begin{array}{c}
CH_3 \\
| \quad S \\
CH_3 \text{—} C \text{—} CHCOCSCH_3 \rightarrow \\
| \quad | \\
CH_3 \quad CH_3 \\
\text{LXXVIII}
\end{array}
\quad
\begin{array}{c}
CH_3 \\
| \\
CHC(CH_3)\text{=}CH_2 \\
| \\
CH_3
\end{array}
$$

dimethylcyclobutylcarbinol was pyrolyzed at 100–120° to give a mixture of isopropenylcyclobutane and isopropenylidenecyclobutane.[75] The S-methyl xanthate of (—)-3-ethoxy-2-methyl-2-butanol (LXXIX) gave (+)-3-ethoxy-2-methyl-1-butene in 71% yield.[8] The S-methyl xanthate (LXXX)

$$(CH_3)_2CCH(CH_3)OC_2H_5 \rightarrow CH_2\text{=}CC(CH_3)_2OC_2H_5$$
$$| \\
OCSCH_3 \\
\| \\
S$$
$$\text{LXXIX}$$
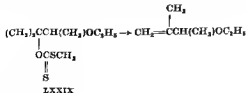
[75] Van Volkenburgh, Greenlee, Derfer, and Boord, *J. Am. Chem. Soc.*, **71**, 172 (1949).

[76] Kasansky, *Ber.*, **69**, 950 (1936).

of dimethylcyclohexylcarbinol was pyrolyzed at 150° to give both the *exo* olefin (11%) and the methylene compound (40%).[36]

$$(CH_3)_2C-OCSCH_3 \quad\quad C(CH_3)_2 \quad\quad CH_3CH=CH_2$$
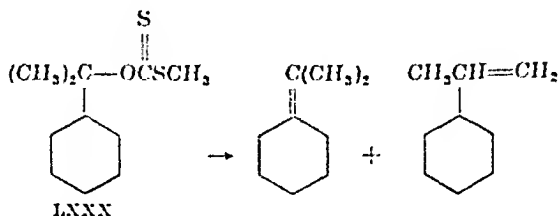
LXXX

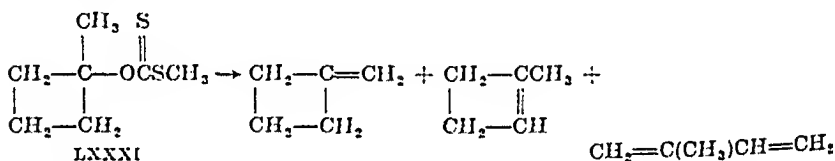**Alicyclic Tertiary Alcohols.** The pyrolysis at 255° of 1-methylcyclobutyl S-methyl xanthate (LXXXI) gave results comparable to those obtained with cyclobutyl S-methyl xanthate. The product, obtained in 86% yield, consisted of methylenecyclobutane (15%), 1-methylcyclobutene (21%), and isoprene (49%).[89]
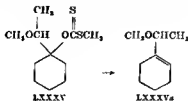
$$CH_2-C-OCSCH_3 \rightarrow CH_2-C=CH_2 + CH_2-CCH_3 +$$
$$CH_2-CH_2 \quad\quad CH_2-CH_2 \quad\quad CH_2-CH$$

LXXXI

$$CH_2=C(CH_3)CH=CH_2$$

The pyrolysis of the S-methyl xanthates of several 1-alkylcyclohexanols gave olefin mixtures in yields of 46–51%.[36] Analysis of the olefin mixtures showed that the elimination proceeded so as to avoid forming a double bond *exo* to the six-membered ring, and that increasing substitution on the carbinol carbon atom, or the carbon atom adjacent to it, decreased the stability of the xanthate, probably owing to relief of steric crowding in the olefin.

$$R'CH \quad OCSCH_3 \quad\quad C \quad\quad CHR'$$

(LXXXII)   R' = R'' = H
(LXXXIII) R' = CH_3, R'' = H
(LXXXIV)   R' = R'' = CH_3
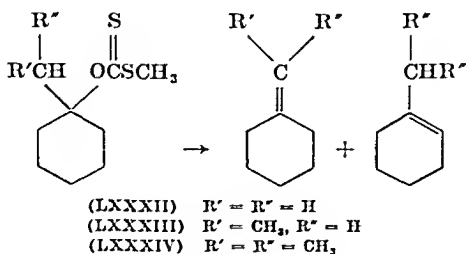
Thus the yields of olefins from the methylcyclohexyl compound LXXXII at 200° were 10% *exo* and 39% *endo*; from the ethyl compound LXXXIII at 200°, 6% *exo*, and 46% *endo*; and, from the isopropyl compound LXXXIV at 100°, 10% *exo* and 36% *endo*.[36]
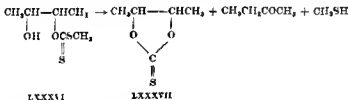
[89] Semenow, Cox, and Roberts, *J. Am. Chem. Soc.*, **78**, 3221 (1956).

The S-methyl xanthate (LXXXV) of (+)-I-(I'-methoxyethyl)-1-cyclo-hexanol gave only the *endo* olefin LXXXVa.[81]

$$
\begin{array}{ccc}
& CH_3 \quad S & \\
& | \quad\quad \| & \\
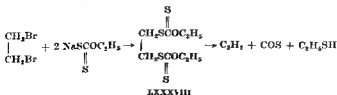CH_3OCH & OCSCH_3 & CH_3OCHCH_2 \\
\end{array}
$$

LXXXV → LXXXVa

Xanthates of Glycols

The only unambiguous example of the use of a glycol in the Chugaev reaction is the pyrolysis of the mono-S-methyl xanthate (LXXXVI) of 2,3-butanediol.[82,83] The major product after extended heating at 200° was the cyclic thionocarbonate LXXXVII[82,83] accompanied by a trace of methyl ethyl ketone presumably derived from the enol formed by elimination.[82]

$$
CH_3CH—CHCH_3 \rightarrow CH_3CH—CHCH_3 + CH_3CH_2COCH_3 + CH_3SH
$$

$$
\begin{array}{cc}
| \quad\quad | & \quad\quad O \quad O \\
OH \quad OCSCH_3 & \quad\quad \backslash \; / \\
\quad\quad \| & \quad\quad C \\
\quad\quad S & \quad\quad \| \\
& \quad\quad S
\end{array}
$$

LXXXVI

LXXXVII

Several xanthates of 1,2-dithioglycols reportedly gave acetylenes and a variety of other products. Ethylene dibromide was treated with sodium O-ethyl xanthate, and the resulting dixanthate LXXXVIII was pyrolyzed

$$
\begin{array}{cc}
& S \\
& \| \\
CH_2Br & CH_2SCOC_2H_5 \\
| \quad + 2\ NaSCOC_2H_5 \rightarrow & | \rightarrow C_2H_2 + COS + C_2H_5SH \\
CH_2Br & CH_2SCOC_2H_5 \\
\| & \| \\
S & S
\end{array}
$$

LXXXVIII

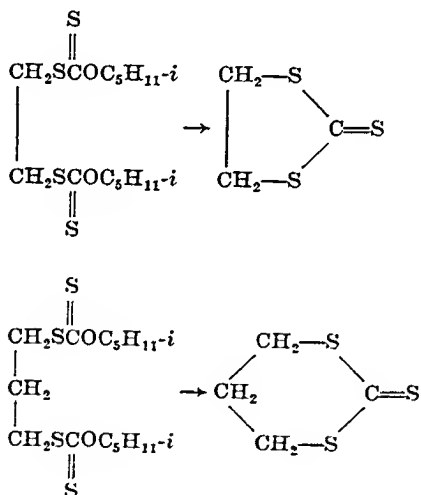[81] Levine and Karten, *J Biol Chem*, **113**, 55 (1936).
[82] Fomin, *J. Gen Chem* (*U S S R*), **5**, 1192, (1935) [*C.A.*, **30**, 1745 (1936)].
[83] Stevens and Richmond, *J Am Chem Soc*, **63**, 3132 (1941).

at 200–270° to give acetylene (26%), carbon oxysulfide, and ethyl mercaptan.[84, 85]

In a similar fashion, 1,2-dibromopropane gave a dixanthate which yielded methylacetylene, carbon disulfide, carbon oxysulfide, ethanol, and ethyl mercaptan;[84, 85] and 1,2-dibromobutane afforded ethylacetylene.[84] 2,3-Dibromobutane, treated in the same manner, gave butadiene,[84] as did 1,4-dibromo-2-butene.[85] The formation of ethyl mercaptan in these pyrolyses suggests that the xanthate is partially undergoing pyrolysis in the normal fashion, and that ethylene and a 1,2-dithiol should also be formed.

In direct contrast to these pyrolyses, the pyrolysis of the xanthates shown below gave cyclic trithiocarbonates and other unidentified products.[86] A number of related xanthates were also prepared, but the pyrolyses were not described.

$$\begin{array}{ccc}
\overset{\text{S}}{\overset{\|}{\text{CH}_2\text{SCOC}_5\text{H}_{11}\text{-}i}} & \text{CH}_2\text{—S} & \\
| & & \diagdown \\
| & \rightarrow \quad | & \quad \text{C}\!=\!\text{S} \\
| & & \diagup \\
\overset{}{\underset{\overset{\|}{\text{S}}}{\text{CH}_2\text{SCOC}_5\text{H}_{11}\text{-}i}} & \text{CH}_2\text{—S} &
\end{array}$$

$$\begin{array}{ccc}
\overset{\text{S}}{\overset{\|}{\text{CH}_2\text{SCOC}_5\text{H}_{11}\text{-}i}} & \text{CH}_2\text{—S} & \\
| & \diagup \quad \diagdown \\
\text{CH}_2 & \rightarrow \text{CH}_2 \quad\quad \text{C}\!=\!\text{S} \\
| & \diagdown \quad \diagup \\
\overset{}{\underset{\overset{\|}{\text{S}}}{\text{CH}_2\text{SCOC}_5\text{H}_{11}\text{-}i}} & \text{CH}_2\text{—S} &
\end{array}$$

Further investigation of the use of glycols in the Chugaev reaction seems desirable, since potentially the reaction could provide a good synthetic route to acetylene derivatives and conjugated dienes.

COMPARISON WITH OTHER METHODS OF DEHYDRATION

The most general and widely used method for dehydration of alcohols to olefins is to use an acid, such as sulfuric, phosphoric, or p-toluenesulfonic. Since these reagents may promote a carbonium ion type of reaction under

the usual conditions, rearrangement of the carbon skeleton frequently occurs [84] Solvolytic eliminations employing sulfonate esters of alcohols possess the same disadvantage In such cases, the Chugaev reaction is quite valuable since rearrangements are rare.

If other acid-sensitive functional groups are also present in the alcohol, the Chugaev reaction, utilizing basic conditions, is advantageous

Although vapor phase dehydration of alcohols over aluminum oxide may be superior to acid dehydration in the liquid phase, the high temperatures required (300–500°) render the method useless for compounds which cannot be vaporized readily or undergo decomposition or rearrangement.[87] These disadvantages are minimized at the much lower temperatures (100–250°) employed for the Chugaev method

A dehydration method closely related to the Chugaev reaction is the pyrolysis of carboxylic esters, commonly the acetate esters. Although such esters undergo elimination via the same type of cyclic transition state as do xanthates, they are more stable to pyrolysis and require temperatures in the range 300–600° They offer the considerable advantages, however, that in general they are much easier to prepare from alcohols than are the xanthates, and the olefins are less likely to be contaminated by the other decomposition products. A serious disadvantage of the Chugaev reaction is that the olefins are frequently contaminated with sulfur-containing impurities, which are usually removed by distillation from sodium metal with an accompanying decrease in yield

Carbonate and carbamate esters' fall between the xanthate and carboxylic esters in stability toward pyrolysis and are easier to prepare than xanthates The carbonate esters possess the additional advantage that the other decomposition products, carbon dioxide and an alcohol (commonly ethyl), are neutral, do not react with the olefins formed, and do not have offensive odors However, these esters have not found widespread use

Esters of boric acid are sometimes quite easy to pyrolyze,[88] but further investigation of this method is necessary before its generality can be assessed

In summary, the Chugaev reaction offers advantages when it is necessary to employ low temperatures, basic reaction conditions, or to avoid rearrangements. The disadvantages are the difficulties sometimes encountered in the preparation and purification of the xanthate esters, and in the removal of sulfur-containing impurities from the olefin.

In general, ester pyrolyses of all types offer high stereo-selectivity because of the restrictions on the orientation of groups necessary to form

[87] Dixon, Cook, and Whitmore, *J Am Chem Soc*, **70**, 3361 (1948).

[88] O'Connor and Nace, *J Am Chem Soc*, **77**, 1578 (1955)

the cyclic transition state. The combination of the pyrolysis method with the base-catalyzed *trans* elimination of sulfonate esters of alcohols provides two stereospecific methods for obtaining *cis* or *trans* eliminations.

EXPERIMENTAL CONDITIONS

Preparation of the Xanthates

The utility of the Chugaev reaction is partially dependent upon the ease of formation and purification of the xanthate. The most commonly encountered difficulty in the preparation of xanthates is formation of the metal salt of the alcohol. The method usually employed consists in heating a solution of the alcohol in ether, benzene, or toluene under reflux with metallic sodium or potassium. The substitution of sodium hydride[40,49c,80] for the metal may result in higher yields, especially with less reactive alcohols such as sterols.[17] The use of sodium amide in toluene has also been reported,[9] and the method is convenient in that salt formation can be followed by observing the ammonia evolution.

Sodium salt formation has also been accomplished by means of the exchange reaction between potassium *sec*-amyloxide[89] or *t*-amyloxide.[33,90]

It was reported that the yield of xanthate produced by use of powdered sodium or potassium hydroxide with an excess of the required alcohol was superior to that produced by use of sodium or potassium metal.[25] However, in a later study it was stated that no essential difference in yield of xanthate was obtained.[36]

In one instance, where sodium hydride was used to form the sodium salt of the alcohol, epimerization of the alcohol was observed. When α-cholestanol in benzene was heated under reflux with sodium hydride and then treated with carbon disulfide and methyl iodide, β-cholestanyl S-methyl xanthate was obtained in 65% yield.[17] When the reaction was attempted under an atmosphere of dry nitrogen, only α-cholestanol was recovered.

Such epimerization of alcohols may occur more frequently than is realized, and the presence of the isomeric xanthate could account for some of the reports of apparent *trans* Chugaev eliminations.

Once the metal salt is obtained, difficulty is rarely encountered in the subsequent reactions with carbon disulfide and the alkyl halide (usually methyl iodide). However, in the attempted preparation of cholesteryl S-isobutyl xanthate, no xanthate could be obtained, probably owing to steric hindrance to back-side attack by the sodium xanthate on the isobutyl iodide.[7]

[89] Chugaev and Gasteff, *Ber.*, **42**, 4631 (1909).

[90] Chugaev, *J. Russ. Phys. Chem. Soc.*, **36**, 1253 (1904) [*Chem. Zentr.*, **1905**, I, 525].

Difficulty is frequently encountered in the purification of the xanthate. Many xanthates are too unstable to permit purification by distillation, even under reduced pressure. Unless these xanthates can be obtained in crystalline form, purification is limited to washing with water to remove inorganic salts and unreacted alcohols of low molecular weight. Occasionally chromatography on alumina can be used for purification of liquid xanthates. Many of the xanthates listed in Tables II through IV were liquids which could not be purified, and the crude xanthates were pyrolyzed directly.

In at least one case [(−)-menthyl S-methyl xanthate] instability of the xanthate to ultraviolet light was noted [73] This observation suggests that, if a xanthate is to be stored for any length of time before pyrolysis, it should be protected from light

Decomposition of the Xanthates

The pyrolysis of the xanthate is usually carried out by distilling it under atmospheric pressure. Depending on the pyrolysis temperature and the boiling point of the olefin, it will either distill with the other decomposition products or remain behind in the reaction flask. Sulfur-containing impurities may be removed by heating the olefin under reflux with sodium metal.

It is sometimes advantageous to conduct the pyrolysis under reduced pressure, thus ensuring that the olefin and other decomposition products are removed as fast as they are formed. This method reduces the contamination of the olefin by sulfur-containing impurities since it is known that mercaptans will add to olefins at elevated temperatures.[91]

If the stability of the olefin is such that it distills unchanged at its boiling point, decomposition can be effected by dropwise addition of the xanthate to boiling diphenyl ether[49] or some other high-boiling inert compound

EXPERIMENTAL PROCEDURES

(−)-Menthyl S-Methyl Xanthate (Use of Metallic Sodium) [1,73] To a solution of 50 g. (0.31 mole) of (−)-menthol in 59 ml. of toluene is added 8 g. (0.35 gram atom) of sodium. The mixture is heated under reflux for 32 hours. The mixture is then cooled in an ice bath, the unreacted sodium is removed with a wire, and 125 ml. of anhydrous ether is added followed by 45 g. of carbon disulfide. When the resultant reaction has subsided, 45 g. of methyl iodide is added, the mixture is heated under reflux for 1

n Bichonbottom, Reactions of Organic Compounds 2nd ed., p. 30, Longmans, Green and Co., London, 1948

hour and then cooled and filtered. The precipitated sodium iodide is washed with ether and the washings added to the filtrate. The solvent is then removed at 40°/20 mm. and the residue is taken up in 100 ml. of ethanol. Water is added to the point of cloudiness, crystallization is induced by scratching, and the mixture is cooled. The first crop, 33.4 g., has m.p. 40–40.5°, $[\alpha]_D - 80°$ (1% in $CHCl_3$); the second crop, 10 g., m.p. 40–40.5°, $[\alpha]_D - 84°$ (1% in $CHCl_3$); the third crop, 7 g., m.p. 39–40.5° (total yield, 65%).

A 10.0-g. (0.041 mole) sample of the xanthate is heated under reflux at 145–155° for 6 hours. The residue is then distilled through an efficient semimicro column[92] to give 3.23 g. (56%) of menthenes, b.p. 64.5–65°/22 mm., n_D^{25} 1.4500, $[\alpha]_D + 117°$ (1% in $CHCl_3$). After a sample is epimerized,[93] it has $[\alpha]_D + 32°$ (1% in $CHCl_3$), which corresponds to 24% of 2-menthene in the original mixture.

Cyclobutyl S-Methyl Xanthate (Use of Sodium Hydride).[40] To a stirred suspension of 3.5 g. (0.146 mole) of sodium hydride in 100 ml. of dry ether is added dropwise 8 g. (0.11 mole) of cyclobutanol. The resulting mixture is heated under reflux for 3 hours. Then 9.7 g. (0.135 mole) of carbon disulfide is added, the mixture is heated under reflux for 3 hours, 19.2 g. (0.135 mole) of methyl iodide is added, and the mixture is heated under reflux for an additional 3 hours. Water is then added to dissolve the solid material, the ether layer is separated and dried, and the ether removed. Distillation at 67°/1.5 mm. yields 14.3 g. (84%) of the xanthate.

The xanthate is pyrolyzed by adding it dropwise to boiling biphenyl to yield butadiene, collected as a gas at atmospheric pressure. The yield is quantitative.

Cyclopentanol, when subjected to the same procedure, gives the xanthate, b.p. 88°/2.5 mm., in 90% yield. Pyrolysis of the xanthate furnishes cyclopentene, collected as the dibromide, in 70% yield.

Methyl-*t*-butylcarbinyl S-Methyl Xanthate (Use of Potassium *t*-Amyloxide).[33] A mixture of 42.9 g. (1.1 gram atoms) of potassium, 85.8 g. (1.1 moles) of *t*-amyl alcohol, and 1.5 l. of toluene is boiled under reflux until the potassium has reacted. Then 102 g. (1 mole) of methyl-*t*-butylcarbinol is added to the hot solution. The solution is cooled and 115 g. (1.5 moles) of carbon disulfide is slowly added, causing the precipitation of the yellow potassium xanthate and the evolution of much heat. The mixture is cooled to room temperature, 156 g. (1.1 moles) of methyl iodide is added, and the mixture is heated on a steam bath for 4–5 hours. The mixture is then filtered to remove the potassium iodide,

[92] Gould, Holzman, and Niemann, *Anal. Chem.*, **20**, 361 (1948).

[93] Barton, Head, and Williams, *J. Chem. Soc.*, **1952**, 453.

and the filtrate is distilled at 70 mm to remove toluene and alcohol. The residue is distilled in a Claisen flask to give the xanthate, b.p. 85–87°/6 mm., in 74%, yield. The methyl iodide may be replaced by an equivalent amount of dimethyl sulfate with equally good results.

The xanthate is pyrolyzed by distillation at atmospheric pressure to give t-butylethylene in 58%, yield

When the same procedure is applied to methyl-t-amylcarbinol, ethyl-t-butylcarbinol, ethyl-t-amylcarbinol, and n-propyl-t-butylcarbinol, the xanthates are obtained in yields of 41–75%, and on pyrolysis they give the corresponding olefins in yields of 55–73%,

Isoamyl S-Methyl Xanthate (Use of Sodium Hydroxide).[23] A mixture of 40.5 g. (1 mole) of finely pulverized sodium hydroxide, 89 g. (1 mole) of isoamyl alcohol, 50 ml. of carbon tetrachloride, and 600 ml. of ether is stirred for 30 minutes, and then 76 g. (1 mole) of carbon disulfide is added, followed by 149 g. (1.05 mole) of methyl iodide. Distillation gives 126 g. (71%) of isoamyl S-methyl xanthate, b.p. 100–102°/10 mm., n_D^{20} 1.5234.

The substitution of potassium hydroxide for sodium hydroxide does not affect the yield, elimination of the solvent and the use of excess alcohol gives a slightly higher yield. The use of potassium metal, isoamyl alcohol, and xylene gave the same xanthate in 65% yield.

The xanthate (216 g., 1.2 moles) is heated at its boiling point under partial reflux for 7.5 hours and 45 g. of distillate is collected. After purification by three extractions with 40% potassium hydroxide solution and one with saturated mercuric chloride solution, distillation gives isopropylethylene, b.p. 19–20°/740 mm., in 15% yield.

3β-Cholestanyl S-Methyl Xanthate.[17] A mixture of 1.0 g. (2.6 mmoles) of 3β-cholestanol, 500 mg. (20.8 mmoles) of sodium hydride, and 50 ml. of dry benzene is stirred and heated under reflux for 24 hours The reaction mixture is then allowed to cool to room temperature, 4 ml of carbon disulfide is added, and the resulting red mixture is stirred under reflux for 24 hours. It is then cooled to room temperature, 4 ml of methyl iodide is added, and the mixture is stirred and heated under reflux for 24 hours. Water is added dropwise to decompose the excess sodium hydride, the organic layer is washed with water, dried over anhydrous sodium sulfate, and the solvent is evaporated on a steam bath. The residue is taken up in 10 ml. of petroleum ether (b.p. 30–60°) and chromatographed on 10 g. of aluminum oxide (Merck, for chromatographic adsorption) On elution with 50 ml of petroleum ether the xanthate is obtained as a yellow oil which crystallizes when solvent-free Recrystallization from 2:1 acetone-ethanol gives 950 mg. (77%) of 3β-cholestanyl S-methyl xanthate, m.p. 86–87°, $[\alpha]_D + 5°$ (1%, $CHCl_3$).

One more recrystallization from 1:1 acetone-ethanol gives 800 mg. (65%) of analytically pure material, m.p. 87.5–88°, $[\alpha]_D + 2°$.

The xanthate (214 mg., 0.447 mmole) is pyrolyzed by heating at 230°/ 20 mm for 2.5 hours, and the residue is dissolved in petroleum ether and chromatographed on alumina. Petroleum ether elutes 156 mg. (94%) of a one-to-one mixture of 2- and 3-cholestene, m.p. 68–69°, $[\alpha]_D + 64°$, after one recrystallization from one-to-one alcohol-acetone.

TABULAR SURVEY

In Table II and III are listed the xanthates of alcohols that have been pyrolyzed to yield olefins. Table IV is a list of xanthates of glycols and dithioglycols.

Arrangement of compounds within a table is in the order: primary, secondary, and tertiary alcohols. Within each group the compounds are listed according to the number of carbons in the parent alcohol.

The literature has been searched through 1958, but some later references are included.

TABLE II
Pyrolysis of S-Methyl Xanthates of Acyclic Alcohols

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp, °C	Olefin (Yield, %)	References
	Primary Alcohols				
C_5	n-Amyl alcohol	57, 42	Reflux	1-Pentene (15)	25
	Isoamyl alcohol	*	Reflux	Isopropylethylene (15)	25
	Neopentyl alcohol	*	Heat	No olefin, xanthate rearranged to dithiocarbonate (70)	26
C_7	Benzyl alcohol	29	Not given	Stilbene (24)	28
	Cyclohexylcarbinol		100–185	Stilbene (20)	27
C_{10}	4-Methylcyclohexylcarbinol	†	>200	Methylenecyclohexane	20
	Diacetone galactose		Not given	Methylene-4-methylcyclohexane	29
			Not given	Unidentified products	30
	Secondary Alcohols				
C_5	2,3,4,14,14-Ventafluoro-2-butanol	50	151–152	No reaction	94
C_5	3-Pentanol	24	250	2-Pentene (cis, 34; trans, 55)	31
	Methylcyclopropylcarbinol	52	150–230	Vinylcyclopropane (42), 1,1-penta-diene, 1-cyclopropylethyl methyl dithiocarbonate	34
C_6	3-Hexanol	25	250	3-Hexene (cis, 13; trans, 28), 2-hexene (cis, 13; trans, 29)	31
C_7	Methyl t-butylcarbinol	74	160–175	3-Methyl-2-hexene (71)	4, 33
	Ethylisobutylcarbinol	30	200	2-Methyl-1,3-hexene (cis, 5; trans, 43), 4-methyl-2-hexene (cis, 9; trans, 29)	31

Note: References 91 to 100 on p. 100.

* The xanthate was isolated and purified, but no yield was given

† The crude xanthate was pyrolyzed.

TABLE II—*Continued*

PYROLYSIS OF S-METHYL XANTHATES OF ACYCLIC ALCOHOLS

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
	Secondary Alcohols (Continued)				
C₇ (*Cont.*)	Methyl-t-amylcarbinol	75	Not given	l-Amylethylene (67)	33
C₈	Ethyl-t-butylcarbinol	60	Not given	2,2-Dimethyl-3-pentene (73)	33
	Trifluoromethyl-n-hexylcarbinol	*	241–243	No reaction	95
	Methylcyclohexylcarbinol	57	250	Cyclohexylethylene (32), ethylidenecyclohexane (20)	36
	2-Octanol	†	165	1-Octene (23–25), 2-octene (21–23)	25
	Ethylneopentylcarbinol	†	150	2,2-Dimethyl-3-hexene (cis, 2; trans, 58), 2,2-dimethyl-4-hexene (cis, 5; trans, 21)	31
	2,2-Dimethyl-3-hexanol	63	200	trans-2,2-Dimethyl-3-hexene (63–82)	31, 33
C₁₀	3,3-Dimethyl-4-hexanol	41	Not given	3,3-Dimethyl-1-hexene (55)	33
	erythro-3-Phenyl-2-butanol	85	180	2-Phenyl-2-butene (cis, 5; trans, 45), 3-phenyl-1-butene (32)	11
	threo-3-Phenyl-2-butanol	80	180	2-Phenyl-2-butene (cis, 27; trans, 8), 3-phenyl-1-butene (28)	11
C₁₁	erythro-2-Phenyl-3-pentanol	75	200	2-Phenyl-2-pentene (cis, 4; trans, 27), 2-phenyl-3-penteno (37)	11
	threo-3-p-Tolylthio-2-butanol	†	200–220	cis-2-p-Tolylthio-2-butene (77)	24

	Alcohol	Temperature		Product	Yield (%)
	erythro-3-p-Tolylthio-2-butanol	200-220	†	trans-3-p-Tolylthio-2-butene (58)	21
	threo-3-p-Tol(sulfonyl)-2-butanol	200-220	†	cis-2-p-Tol(sulfonyl)-2-butene (58)	21
	3-p-Tol(sulfonyl)-2-butanol	200-220	•	3-p-Tol(sulfonyl)-2-butene (cis,38; trans, 19)	21
C₆	1,2-5,6-Diacetone glucose	290-300	•	Xanthate rearranged to dithiocarbonate (30)	30
				Undestroyed product	
C₇	2,3-5,6-Diacetone mannose	Not given	•	Tetraphenylethylene	30
C₁₃	Benzhydrol	190-260	•	Benzalcyclohexane (20)	98
	Phenylcyclohexylcarbinol	160-175	70	cis-1,2-Diphenyl-1-propene (85)	97
C₁₅	threo-1,2-Diphenyl-1-propanol	145-195	71	trans-1,2-Diphenyl-1-propene (77)	13
	erythro-1,2-Diphenyl-1-propanol	130-195	70		13
C₂₃	12 Tricosanol	Not given	†	11-Tricosene	32
	Tertiary Alcohols				
C₇	Dimethylcyclopentylcarbinol	130-135	†	Isopropenylcyclopropane (24)	78
C₇	(−)-2-Methyl-3-ethoxy-2-butanol	Not given	†	(+)-2-Methyl-3-ethoxy-2-butene (71)	5
C₉	Dimethylcyclobutylcarbinol	100-120°	†	Mixture of neopropylidenecyclobutane and isopropenylcyclobutane (87%)	70
C₉	Dimethylcyclohexylcarbinol	150	57	Isopropylidenecyclohexane (11), 2-cyclohexylpropene (40)	30

Note: References 94 to 100 are on p. 100.

• The xanthate was isolated and purified, but no yield was given.

† The crude xanthate was pyrolyzed.

TABLE III

PYROLYSIS OF XANTHATES OF ALICYCLIC ALCOHOLS

(The S-methyl xanthate was used unless otherwise specified.)

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
	Secondary Alcohols				
C_4	Cyclobutanol	84	255	Butadiene (100)	40
C_5	Cyclopentanol	90	255	Cyclopentene (70, as dibromide)	40
C_7	endo-5-Hydroxybicyclo-[2.2.1]-2-heptene	†	250	Bicyclo-[2.2.1]-2,5-heptadiene (5)	76
	3-Methylcyclohexanol	80	Not given	Mixture of 3- and 4-methylcyclo-hexene (70)	41
C_8	4-Methylcyclohexanol	†	175–178	4-Methylcyclohexene (27)	42
	Cycloöctanol	*	135–290°	cis-Cycloöctene (88)	49a
C_9	Camphenilol	50	Reflux	Mixture of apobornylene and apocyclene (55)	50, 51
	trans-2-Carbethoxycyclohexanol	†	210–235	Ethyl cyclohexenecarboxylate (34)	46
	Cyclononanol	*	120–130	Cyclononene (cis, 21; trans, 14)	49
			380	Cyclononene (cis, 24; trans, 20)	
			400	Cyclononene (cis, 30; trans, 7), 1,8-nonadiene	
			450	Cyclononene (cis, 32; trans, 8), 1,8-nonadiene (5)	
			500	cis-Cyclononene (12), 1,8-nonadiene (12)	
C_{10}	cis-2-Methyl-1-indanol	*	98–100	2-Methylindene (20)	10
	trans-2-Methyl-1-indanol	*	98–100	2-Methylindene (80)	10
	cis-α-Decalol-(1) (m.p. 93°)	25	180	1(9)-Octalin and 2-octalin	9, 47
	trans-α-Decalol-(1) (m.p. 40°)	†	205–210	1(9)-Octalin (3), trans-1-octalin (14)	9

	Disulfide†	Temp.	Products	Ref.
trans-Decalol-(1) (m.p. 63°)		100–200	cis- and trans-2-octalin, 9,10-octalin	9, 47
trans-β-Decalol-(1) (m.p. 75°)		150–200	1- and 2-octalin	9, 47
Cyclodecanol		135–220	Cyclodecene (ca. 6 %) trans, 28 (50)	48*
				50(?)
(−)-Borneol		Not given	Bornylene (90 %)	50
		150–200	Bornylene and tricylene	57, 54
		229–230	(−)-Bornylene	55
		190–200 (reduced pressure)	Bornylene (50), "stable xanthate" (50)	51
(+)-Borneol	↑	155–160	Camphene, bornylene, (−) borneol	50
Isoborneol	↑	229–230	(−)-Bornylene	55
(+)-Epiborneol	↑	110–175	(+)-Bornylene	61
(−)-Carvomenthol		Not given	(+)-Bornylene	60
(−)-Carvol		"Dist"	(−)-δ-Bornylene	67
(+)-Dihydrocarveol		"Dist"	(−)-14 Carene	
			Limonene, (−)-β-isolimonene	65, 50, 90
(+)-Dihydrocarveol		170–200	(+)-β-isolimonene	18
x-Fenchol	90	230	Mixture (72) of cyclohexene and x-fenchene	24,
Isofenchol		100–230	x-fenchene, cyclohexene, isofenchylene	81 101
				62 63
(−)-Pinocampheol		170–200	Δ-nd x-Pinene	16, 71, 72
Isopinocampheol		Not given	x-Pinene (38)	72
Thujol		100–100	x- and β-Thujene	19, 21, 72
				68, 69
(+)-Thujol	↑	138	x-Thujene	70
(−)-Thujol	↑	183	β-Thujene	70
(−)-Neothujol	↑	Not given	β-Thujene	70
Verbanol	↑	Not given	"Thujene" (18)	100

Note: References 84 to 100 are on p. 100.

* The xanthate was isolated and purified, but no yield was given.

† The crude xanthate was pyrolyzed.

TABLE III—Continued

PYROLYSIS OF XANTHATES OF ALICYCLIC ALCOHOLS

(The S-methyl xanthate was used unless otherwise specified.)

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
	Secondary Alcohols (Continued)				
C₁₀ (Cont.)	(−)-Menthol	84 ("Stable" xanthate)	145-155	2-Menthene (14), 3-menthene (37)	73
		("Unstable" xanthate)	145-155	2-Menthene (11), 3-menthene (13)	73
		("Unstable" xanthate)*	130-140°/10 mm.	2- and 3-Menthene; "stable" xanthate (40-50)	54, 73
		66	130-200	Menthenes	1, 9, 54, 101-103
		(S-Ethyl)*	Not given	Menthenes	102
		50 (S-Isopropyl)	170	Menthenes	74
			Distillation under reduced pressure	Menthenes; "stable" xanthate (12)	71
		40 (S-Benzyl)	140	Menthenes	71
		(S-p-Nitrobenzyl)*	135	Menthenes	74
		(Dixanthide)†	120	Menthenes, (−)-menthol	1, 50
		(Xanthogen amide)†	200-220	Menthenes	75
	(+)-Neomenthol	†	185-220	2-Menthene (80)	9
	trans-4-t-Butylcyclohexanol	62	208	4-t-Butylcyclohexene	11
	2-t-Butylcyclohexanol	†	200-205	3-t-Butylcyclohexene (60)	43
	Cyclodecanol	†	135-205	Cyclodecene (cis, 6; trans, 38)	19c
	2,2,6-Tetramethylcyclohexanol	†	230	No olefin, rearranged to dithiocarbonate (70-80)	26

Formula	Alcohol	Olefin (% yield)	Temp. (°C)	Yield (%)	References
	Thujamenthol	Thujamenthene	Not given		104
	cis-2-Methyl-1-tetralol	No reaction	98–100		15
	trans-2-Methyl-1-tetralol	2-Methyl-3,4 dihydronaphthalene	98–100		15
	4-Methylbornol	2-Methylbornylene	Not given		105
	4-Methylisobornol	4-Methylbornylene			105
	6-Methylbornol	6-Methylbornylene (52)	210–215		106
	cis-2 Phenylcyclohexanol	2-Phenylcyclohexene (0–3), 3-phenylcyclohexene (68–87)	210–240	90	14, 45
	trans 2 Phenylcyclohexanol	2- and 3-Phenylcyclohexene	110–175		14
	4-Phenylcyclohexanol	4-Phenylcyclohexene (47)	230–240		14
C_{13}	cis-2-p Tolylthiocyclohexanol	p-Tolylthiocyclohexene (3–5), 3-p-tolylthiocyclohexene (49–51)	100–210		23
	trans-2-p-Tolylthiocyclohexanol	p-Tolythiocyclohexene (85)	100–210		23
	cis-2-p-Tolylsulfonylcyclohexanol	p-Tolylsulfonylcyclohexene (40)	210–215		23
	trans 2-p-Tolylsulfonylcyclohexanol	p-Tolylsulfonylcyclohexene (77)	210–215		23
C_{16}	1,1,1-Trimethyl-2 hydroxy-3-diethoxymethylcycloheptane	Undentified olefin (50)	200–210	85	48
C_{27}	Cholestanol	3,5-Cholestadiene (78–93)	200–220		17, 77
		3,5 Cholestadiene (88)	200–220		89, 107, 108
		3,5 Cholestadiene	200	80 (5-Ethyl)†	7, 108
		3,5-Cholestadiene (90)	230	(5-n Propyl)†	7
		3,5-Cholestadiene (90)	230	82 (5-Benzyl)†	7
		3,5 Cholestadiene (88)	220	85 (5-p-Nitenbenzyl)†	7
		3,5 Cholestadiene (84)	220	85 (5-p Chloro-benzyl)†	7
				70 (5-p-Methoxy-benzyl)	

Note: References 94 to 109 are on p. 100.

* The xanthate was isolated and purified, but no yield was given.

† The crude xanthate was pyrolyzed.

TABLE III—*Continued*

PYROLYSIS OF XANTHATES OF ALICYCLIC ALCOHOLS

(The S-methyl xanthate was used unless otherwise specified)

No. of C Atoms	Alcohol	Xanthate Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
	Secondary Alcohols (Continued)				
C_{27} (*Cont.*)	Cholesterol (*Continued*)	80 (S-2,4-Dinitrophenyl)	220	3,5-Cholestadiene (85)	7
		80 (S-Diphenylmethyl)	220	3,5-Cholestadiene (72)	7
		72 (S-Triphenylmethyl)	220	3,5-Cholestadiene (85)	7
		92 (Trithiocarbonate)	220	3,5-Cholestadiene (80)	7
	3β-Cholestanol	77	230	2- and 3-Cholestene (94)	17
		87 (S-Benzyl)	230	2- and 3-Cholestene (92)	17
	Tertiary Alcohols				
C_5	1-Methylcyclobutanol	78	255	Methylenecyclobutane (15), 1-methylcyclobutene (21), isoprene (10)	80
C_7	1-Methylcyclohexanol	†	200	Methylenecyclohexane (10), 1-methylcyclohexene (39)	20, 36
C_8	1-Ethylcyclohexanol	†	200	Ethylidenecyclohexane (6), 1-ethylcyclohexene (46)	36
C_9	1-Isopropylcyclohexanol	†	100	Isopropylidenecyclohexane (10), 1-isopropylcyclohexene (36)	36
	(−)-1-(1'-Methoxyethyl)cyclohexanol	†	Distilled	(−)-1-(1'-Methoxyethyl)cyclohexene	81

Note: References 94 to 100 are on p. 100.

† The crude xanthate was pyrolyzed.

TABLE IV

PYROLYSIS OF XANTHATES OF GLYCOLS AND RELATED COMPOUNDS

Xanthate	Yield, %	Pyrolysis Temp., °C.	Olefin (Yield, %)	References
$CH_3SCSOC_2H_5$ —	*	200–270	Acetylene (20), ethyl mercaptan	84, 85
$CH_3SCSOC_2H_5$ CH_2 —	‡	Not given	Methylacetylene, ethanol, ethyl mercaptan, carbon disulfide, carbon oxysulfide	84, 85
$CH_2SCSOC_2H_5$ — $CH_2SCSOC_2H_5$ (?)	‡	Not given	Butadiene, ethyl mercaptan, carbon oxysulfide	85
$CHClCH_2SCSOC_2H_5$ C_2H_5 —	‡	Not given	Ethyl acetylene, ethyl mercaptan, carbon oxysulfide	84
$CH_3SCSOC_2H_4$ $CH_3CH_2SCSOC_2H_5$	‡	Not given	Butadiene	84
CH_2CHOH $CH_2CHOCSCSH$ S	‡	200	Cyclic thionocarbonate, methyl ethyl ketone	82, 83, 109

Note: References 84 to 109 are on p. 100.
* The xanthate was isolated and purified, but no yield was given.
‡ The crude xanthate was pyrolyzed.

REFERENCES FOR TABLES II–IV

[94] McBee, Higgens, and Pierce, *J. Am. Chem. Soc.*, **74**, 1387 (1952).

[95] Campbell, Knobloch, and Campbell, *J. Am. Chem. Soc.*, **72**, 4380 (1950).

[96] Kursanov, *J. Russ. Phys. Chem. Soc.*, **60**, 921 (1928) [*C.A.*, **23**, 2171 (1929)].

[97] Kursanov, *Ber.*, **64**, 2297 (1931).

[98] Pigulevskii and Gorbunova, *Compt. rend. acad. sci. (U.R.S.S.)*, **54**, 499 (1946) [*C.A.*, **41**, 6551 (1947)].

[99] Chugaev, *Ber.*, **33**, 735 (1900).

[100] Wienhaus and Schumm, *Ann.*, **439**, 20 (1924).

[101] Read and Robertson, *J. Chem. Soc.*, **1926**, 2217.

[102] Chugaev, *J. Russ. Phys. Chem. Soc.*, **35**, 1116 (1903) [*Chem. Zentr.*, **1904**, I, 1347].

[103] Wallach, *Ann.*, **397**, 213 (1913).

[104] Chugaev, *Ber.*, **37**, 1481 (1904).

[105] Shavrygin, *J. Gen. Chem. (U.S.S.R.)*, **7**, 2754 (1937) [*C.A.*, **32**, 2918 (1938)].

[106] Bryusova, *J. Russ. Phys. Chem. Soc.*, **59**, 653 (1927) [*C.A.*, **22**, 2161 (1928)].

[107] Bose and Doran, *J. Chem. Soc.*, **1929**, 2244.

[108] Chugaev and Fomin, *Ann.*, **375**, 288 (1910).

[109] J. H. Richmond, Doctoral Dissertation, McGill University, 1940.

CHAPTER 3

THE SYNTHESIS OF ALIPHATIC AND ALICYCLIC
NITRO COMPOUNDS

NATHAN KORNBLUM*

Purdue University

CONTENTS

INTRODUCTION

This chapter is concerned with the synthesis of nitro compounds in which the nitro group is on a saturated carbon atom. The most important methods available involve:

1. Treatment of alkyl halides with silver nitrite, a reaction useful only for synthesizing primary nitro compounds.

2. The reaction of alkyl bromides and iodides with sodium nitrite, a method of considerable value for the preparation of primary and secondary nitroparaffins and a wide variety of α-nitro esters.

3. The oxidation of amines, a general and very useful means of preparing tertiary nitro compounds which also shows promise as a way of preparing secondary nitro compounds

4 The oxidation of oximes, a method of value for the preparation of a variety of primary and secondary nitro compounds.

5. The nitration of active methylene compounds using nitrate esters under basic conditions.

6 The nitration of active methylene compounds with nitric acid.

The discussion of these methods for introducing a nitro group is followed by a section which takes note of miscellaneous reactions of rather limited utility or reactions about which not much can be said for want of data

Finally, a comparison of the utility of the various methods in the synthesis of particular types of nitro compounds is given (pp 129–130).

Preparations of nitro compounds which employ other nitro compounds as starting materials, e g , Michael condensations of the salts of nitroparaffins and Diels-Alder reactions of nitroolefins, are not discussed. Nor are the liquid or vapor phase nitrations of hydrocarbons taken up, for these usually produce mixtures of products and the emphasis in this chapter is on reactions that readily lead to pure products.

THE REACTION OF ALKYL HALIDES WITH SILVER NITRITE

In 1872 Victor Meyer and Stüber[1] reported that on refluxing isoamyl iodide with silver nitrite a mixture of the nitro compound and isoamyl nitrite was produced Separation of the mixture was readily achieved as a consequence of the considerable difference in boiling points. Other examples were soon forthcoming, and the reaction has come to be regarded as a general one.

$$RX + AgNO_2 \rightarrow RNO_2 + RONO$$

Scope and Limitations

Until recently the reaction was usually conducted in the neighborhood of 80° to 110° However, in 1947 it was shown that the reaction of 2-bromooctane with silver nitrite at such temperatures gives 2-nitrooctane, 2-octyl nitrite, 2-octyl nitrate, 2-octanol, 2-octanone, and other, unidentified, products[2] Soon after, analogous results were obtained with 2-iodobutane.[3] The formation of nitrate esters as by-products in

[1] Meyer and Stüber, *Ber.*, **5**, 203 (1872); Meyer, *Ann.*, **171**, 43 (1874). For a historical account of the discovery of the nitroparaffins see Schaub, *J Chem Educ*, **27**, 557 (1950)
[2] Kornblum, Lichtin, Patton, and Iffland, *J Am Chem Soc*, **69**, 307 (1947).
[3] Kornblum, Patton, and Nordmann, *J Am Chem Soc*, **70**, 746 (1948).

the reaction of cyclopentyl and cyclohexyl iodides with silver nitrite has also been demonstrated recently.[4]

The incursion of side reactions is not limited to reactions in which secondary halides are employed. Thus, after a benzene solution of 1-bromoheptane is heated with silver nitrite at ca. 85°, pure 1-heptyl nitrate is easily isolated.[5]

Nitrate ester formation is a consequence of the thermal instability of silver nitrite which decomposes as follows at 80° or above.[2]

$$2AgNO_2 \rightarrow AgNO_3 + Ag + NO$$
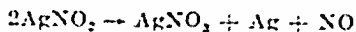
The silver nitrate thus produced reacts readily with alkyl halides to give nitrate esters. Because nitrate esters, in contrast to nitrite esters, are not readily separated from the corresponding nitro compounds by distillation, their formation constitutes a considerable liability.

Primary Nitro Compounds. With primary bromides and iodides side reactions are completely suppressed by starting the reaction at 0° and allowing it to proceed to completion at room temperature.[6] This is an excellent way to prepare pure primary nitro compounds. For example, 1-nitroöctane is obtained in 80% yield from 1-bromoöctane, and 1-iodo-heptane gives 1-nitroheptane in 82% yield.[6] In contrast, primary chlorides are unaffected by silver nitrite at room temperature.

$$CH_3(CH_2)_7Br + AgNO_2 \rightarrow CH_3(CH_2)_7NO_2$$
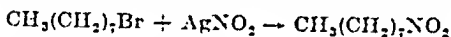
Good yields of nitroparaffins are also obtained with branched-chain primary bromides and iodides in which the branching is β to the carbon atom holding the halogen. Thus isoamyl bromide and iodide give 3-methyl-1-nitrobutane in 72% and 78% yield, respectively. However, branching α to the carbon atom holding the halogen has a deleterious effect. The reaction employing isobutyl iodide produces a distinctly lower yield (55–63%) of nitro compound. When isobutyl bromide is treated with silver nitrite, even after five days only 37% of the bromide has reacted. Finally, neopentyl iodide is not noticeably affected by silver nitrite after three days at room temperature; by this time a typical straight-chain primary iodide has reacted completely.[6] In acetonitrile (see p. 108), at 40°, the reaction between neopentyl iodide and silver nitrite is 85% complete after five days. Only 3% of the product is soluble in base, and efforts to isolate nitroneopentane did not succeed.[7] It is highly unlikely that the reaction of neopentyl iodide with silver nitrite will serve as a means of preparing nitroneopentane.

[4] Kornblum and Teitelbaum, *J. Am. Chem. Soc.*, **74**, 3076 (1952).
[5] M. Cenker, Ph.D. Thesis, Purdue University, 1949.
[6] Kornblum, Taub, and Ungnade, *J. Am. Chem. Soc.*, **76**, 3209 (1954).
[7] N. Kornblum and D. C. Iffland, Unpublished work.

With *para*-substituted benzyl bromides, as shown in Table I, the relative proportions of nitro compound and nitrite ester produced depend on the electrical character of the substituent.[6]

TABLE I

PRODUCTS OF THE REACTION OF SILVER NITRITE WITH BENZYL BROMIDES

Bromide	Nitro Compound, %	Nitrite Ester, %
p-Nitrobenzyl	75	5
Benzyl	61	28
p-Methylbenzyl	45	37
p-Methoxybenzyl	26	55

A number of α,ω dinitro compounds have been prepared by the Victor Meyer reaction. A typical example is the synthesis of 1,4-dinitrobutane[9]

$$ICH_2CH_2CH_2CH_2I + 2AgNO_2 \rightarrow O_2NCH_2CH_2CH_2CH_2NO_2 \quad (41-46\%)$$
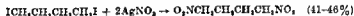
Secondary Nitro Compounds. The reaction of secondary halides with silver nitrite gives poor yields (ca. 15% on the average) of pure nitroparaffins despite the use of temperatures in the range from 0° to 25°.[10] There are several reasons for this behavior.

With secondary halides, nitrite ester formation is more important than in reactions employing primary halides. A second, and major, complication is dehydrohalogenation, which leads to two additional side reactions (a) the "low-temperature" formation of nitrate esters, and (b) the addition of oxides of nitrogen to the olefin.[10]

The following sequence, which accounts for the "low-temperature" production of alkyl nitrates, is consistent with all the facts[*] and invokes only reactions known to occur under the conditions employed.

sec-Alkyl iodide + AgNO₂ → olefin + AgI + HNO₂
2HNO₂ ⇌ H₂O + N₂O₃
N₂O₃ ⇌ NO₂ + NO
AgNO₂ + NO₂ → AgNO₃ + NO
sec-Alkyl iodide + AgNO₃ → *sec*-alkyl nitrate
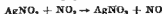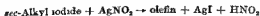
⁶ Kornblum, Smiley, Blackwood, and Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

⁹ Feuer and Leston, *Org. Syntheses*, **34**, 37 (1954).

¹⁰ Kornblum, Smiley, Ungnade, White, Taub, and Herbert, *J. Am. Chem. Soc.*, **77**, 5528 (1955).

* Among them is the fact that oxides of nitrogen are not observed in the reactions of primary straight chain halides with silver nitrite, but they are copiously noted in reactions involving secondary bromides and iodides.

Actually, the yields of nitrate esters are usually less than 10%, but their removal from nitro compounds requires a chemical separation which gives the pure nitroparaffin but significantly depresses the yield.[2, 11]

The addition of oxides of nitrogen to the olefin formed by dehydrohalogenation is evidenced by the formation of relatively non-volatile, thermally unstable products. In several instances crystalline compounds having the composition and properties of N_2O_3-olefin adducts have been isolated.[10] That these adducts are produced under the conditions of the Victor Meyer reaction is not surprising since, under similar conditions, nitrogen trioxide and nitrogen tetroxide readily add to olefins giving nitroso-nitro compounds, nitroso-nitrates, nitro-nitrites, nitro-nitrates, and dinitro compounds.[12]

Tertiary Nitro Compounds. The reaction of tertiary halides with silver nitrite is of no value for the synthesis of tertiary nitro compounds.[10] At best, the nitro compound is obtained in 5% yield; usually none can be isolated.

Tertiary chlorides, in contrast to primary and secondary chlorides, react readily. Here, and with tertiary bromides, the major product is the nitrite ester (ca. 50-60% yield). Just as with secondary halides, blue-green nitrogen oxide–olefin adducts are also produced in appreciable amounts.

When t-butyl iodide is treated with silver nitrite at 0° a rapid reaction takes place. Iodine (50% yield) and a colorless unidentified gas are produced,[10] but the tertiary nitrobutane is not found and the product does not possess the characteristic ultraviolet absorption spectrum of t-butyl nitrite.

It has been reported that camphene hydrochloride I gives the tertiary nitro compound II on treatment with silver nitrite.[13] Actually, the nitro compound is not isolated. Instead the crude reaction product is reduced
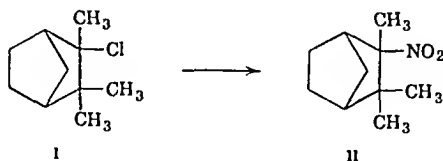
with sodium and isoamyl alcohol to 3-aminoisocamphane which is isolated in an over-all yield of about 4%. For a tertiary halide to give the nitro

[11] Kornblum, W. J. Jones, and Hardies, *J. Am. Chem. Soc.*, to be published.

[12] Baldock, Levy, and Scaifo, *J. Chem. Soc.*, **1949**, 2627; Levy, Scaifo, and Wilder-Smith, *J. Chem. Soc.*, **1946**, 1096.

[13] Stein, Slotzinger, Arnold, Roinhold, Gaines, and Pfister, *J. Am. Chem. Soc.*, **78**, 1514 (1956); Hückel and Nerdol, *Ann.*, **528**, 57 (1937); K. Pfister, Private Communication.

compound is of interest, but even more interesting is the production of the unrearranged product in a system notorious for ease of rearrangement α-Nitro Esters. The reaction of α-bromo esters with silver nitrite is so slow as to be completely impractical Thus, after six and one-half days at room temperature, ethyl bromacetate and ethyl α-bromopropionate reacted only to the extent of 12–15% In contrast, when straight-chain α-iodo esters of low molecular weight are employed, the reaction proceeds at a useful rate and produces excellent yields of pure α-nitro esters.[14]

$$ICH_2CO_2C_2H_5 + AgNO_2 \xrightarrow{48\ hours} O_2NCH_2CO_2C_2H_5 \quad (77\%)$$

$$CH_3(CH_2)_3CHICO_2C_2H_5 + AgNO_2 \xrightarrow{144\ hours} CH_3(CH_2)_3CHICO_2C_2H_5 \quad (84\%)$$
$$\underset{I}{\big|} \qquad\qquad\qquad\qquad\qquad\qquad\qquad \underset{NO_2}{\big|}$$
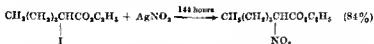
It is not known whether still longer reaction times are necessary with the higher homologs However, the alternative procedure, the reaction between the readily available α-bromo esters and sodium nitrite (p. 112), is so rapid and gives such good yields of α-nitro esters that it is the method of choice. The sole exception is ethyl nitroacetate, which is easily obtained by the silver nitrite reaction but which cannot be prepared by the sodium nitrite process [15]

Stereochemistry and Mechanism

When optically active 2-bromooctane is allowed to react with silver nitrite in diethyl ether, 2-nitrooctane and 2-octyl nitrite are produced with inversion of configuration The same result is obtained with optically active 2-iodooctane [16] If the reaction is conducted in cyclohexane, benzene, or acetonitrile, the 2-nitrooctane and 2-octyl nitrite are again of the inverted configuration [17] The importance of nucleophilic attack rearward to the carbon-halogen bond by nitrite ion is also evident from the fact that neopentyl iodide is inert to silver nitrite under conditions which result in complete reaction with other primary iodides.

The reaction of silver nitrite with aliphatic halides, while possessing these S_N2 attributes, simultaneously exhibits the characteristics of an S_N1 process [a] Thus the reaction rate increases on going from primary to secondary halides Then, too, the variations in rates and products of the reaction of silver nitrite with benzyl bromides as a function of the para

[14] Kornblum, Chalmers, and Daniels, J Am Chem Soc, 77, 6654 (1955)
[15] Kornblum and Weaver, J Am Chem Soc, 80, 4333 (1958)
[16] Kornblum, Fishbein and Smiley, J Am Chem Soc, 77, 6261 (1955)
[17] Kornblum, Hardies, and W J Jones, J Am Chem Soc, to be published

substituent (cf. Table I) become intelligible on the basis that the transition state of these reactions possesses carbonium ion character. That the formation of a silver-halogen bond furnishes an important part of the driving force for these reactions is clear from the failure of sulfonate esters to react with silver nitrite.

Because of these and a number of other facts, the reaction of alkyl halides with silver nitrite is regarded as one in which the pull of the silver on the halogen and the push of the nitrite ion are both important in the transition state; the proportions of S_N1 and S_N2 character vary as a function of the structure of the halide and the nature of the reaction medium, and the products of the reaction reflect this variation in character: the greater the carbonium contribution to the transition state, the greater is the yield of nitrite ester and the smaller is the yield of nitroparaffin.[8]

In contrast, the reaction of optically active α-phenylethyl chloride and silver nitrite proceeds with retention of configuration in ethyl ether or benzene but with inversion in cyclohexane.[17]   These facts are interpreted to mean that, whereas in cyclohexane the graded S_N1–S_N2 path is followed, in diethyl ether (and in benzene) the reaction proceeds via the α-phenylethyl carbonium ion. A detailed discussion of the stereo-chemistry and mechanism of the reaction of silver salts with organic halides will be published shortly.[17]

Experimental Conditions

It is good practice to maintain the reaction mixture in the neighborhood of 0° for the first 24 hours. After this the ice bath is removed and the reaction is allowed to proceed to completion at room temperature. The system should be protected from light until the silver salts are removed by filtration. Also, since nitrite esters are photochemically unstable, it is best to minimize exposure to light until they have been removed from the reaction mixture by distillation.

It is more difficult to remove an alcohol from the corresponding nitro-alkane than it is to separate the nitrite ester. Minimal exposure to a moist atmosphere is, therefore, desirable.

Anhydrous diethyl ether is an excellent medium for these reactions. Petroleum ether, cyclohexane, and benzene have also been employed. In all these media silver nitrite is virtually completely insoluble. In contrast, silver nitrite dissolves in acetonitrile, and when such a solution is treated with 1-iodoheptane the yield of 1-nitroheptane is 60–64% and that of 1-heptyl nitrite is 23–33%.[18] Since the reaction of silver nitrite with 1-iodoheptane in diethyl ether gives 78–82% yields of 1-nitroheptane, and

[18] D. E. Hardies. Ph.D. Thesis, Purdue University, 1957.

only 7–12% yields of 1-heptyl nitrite, it is clear that there is no advantage in carrying out the reaction in acetonitrile.

Indeed, the use of acetonitrile as a solvent is disastrous when a primary nitro compound of relatively high acidity is being produced. Thus, whereas the reaction of *p*-nitrobenzyl bromide with silver nitrite gives *p*-nitrophenylnitromethane in 75% yield in diethyl ether, in acetonitrile no *p*-nitrophenylnitromethane is isolated. Instead, a complex mixture is obtained. Enough is known about the mixture to suggest that the *p*-nitrophenylnitromethane initially formed is converted to the salt by dissolved nitrite ions, the anions of *p*-nitrophenylnitromethane are then oxidized by the silver ions or else undergo nitrosation. In diethyl ether, presumably because of the insolubility of silver nitrite and the much smaller dielectric constant, *p*-nitrophenylnitromethane is not converted to the salt and side reactions are thereby averted.

It is important to recognize that many of the older preparations (prior to 1947) of nitro compounds are likely to be contaminated with the corresponding nitrate esters.[a] Indeed, if in the preparation of a nitro compound the reaction temperature exceeds 30°, the product should be scrutinized carefully to ensure that the corresponding nitrate ester is not present. With a secondary halide, even when the temperature is maintained between 0° and 25°, small amounts of nitrate esters are likely to be formed. Gross contamination by alkyl nitrates is easily demonstrated by shaking the product with 10–20% aqueous alkali; any nitrate ester present remains undissolved. The infrared spectra of nitrate esters are characterized by two sharp, intense, absorption bands close to 6.14 μ and 7.84 μ, and a third, intense but broad band centered around 11.5–11.7 μ.[b] These bands provide a valuable means of detecting even small amounts of alkyl nitrates in nitroalkanes.

THE REACTION OF ALKYL HALIDES WITH SODIUM NITRITE

The widely held view that the reaction of alkali metal nitrites with alkyl halides produces nitrite ester, with little or none of the nitro compound being formed,[c] has recently been shown to be erroneous[d] Actually, the nitro compound and nitrite ester are both produced, but the nitro compound is the major product so that the reaction employing

[a] W. M. Weaver, Ph.D. Thesis, Purdue University 1954
[b] Korolitov, *Compende and Scudny J. Org. Chem.* 22, 377 (1952)
[c] Although statements to the effect occur in many textbooks and monographs, we have been unable to find any except for the view in the original literature
[d] Korolitov, Lamon, Blackwood Mathews Rizoto and Graham *Chem. & Ind.* (London) 1955, 443 ; *J. Am. Chem. Soc.* 78, 1497 1956

sodium nitrite provides a simple and effective means of preparing aliphatic
and alicyclic nitro compounds.

$$RX + NaNO_2 \rightarrow RNO_2 + RONO \qquad (1)$$
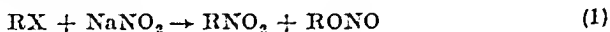
Scope and Limitations

Unless appreciable amounts of *both* the alkali metal nitrite and the
alkyl halide are in solution the reaction does not occur. Dimethyl-
formamide (DMF) and dimethyl sulfoxide (DMSO) are among the few
solvents which dissolve significant amounts of sodium nitrite and alkyl
halides, and this is one of the reasons the synthesis of nitroparaffins from
sodium nitrite and alkyl halides is conducted in these solvents.

A second reason for employing DMF or DMSO is that the reaction of
alkali nitrites with alkyl halides is exceptionally fast in these media.[21, 22]
The great speed of reaction (1) in DMF and DMSO makes it possible to
minimize the side reaction (2) whose existence has been established
recently.[23]

$$RR'CHNO_2 + RR'CHONO \xrightarrow{NaNO_2} RR'C(NO)NO_2 + RR'CHOH \qquad (2)$$
$$(R = alkyl; \; R' = alkyl \; or \; hydrogen)$$
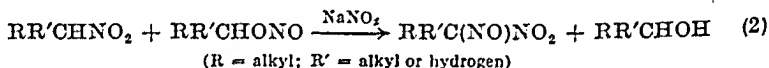
Even in DMF, sodium nitrite has a rather limited solubility, and this
prevents realization of the reaction of nitrite ion with an alkyl halide at
a rate which is anticipated from the kinetics in dilute solution. None the
less, the reaction of a primary bromide or iodide with sodium nitrite is so
much faster than the competing side reaction (2) that the side reaction can
be effectively forestalled by working up the reaction mixture promptly.

With secondary bromides and iodides, nitrosation of the initially
formed nitroparaffin would become a serious problem in the absence of
several simple devices. The addition of urea to DMF markedly increases
the solubility of sodium nitrite and, in reactions employing secondary
alkyl iodides, this is all that is required to prevent the nitrosation process
of equation (2).

With secondary bromides and also cyclopentyl and cycloheptyl iodides,
it becomes desirable not only to add urea but also a nitrite ester scavenger.
Compounds such as phloroglucinol, catechol and resorcinol can be used
for this purpose. Of these, phloroglucinol is the most effective.[21] Sodium
nitrite is so soluble in DMSO that urea is never added when DMSO is the
reaction medium.[22]

Alkyl bromides and iodides are equally useful for the preparation of

[21] Kornblum and Powers, *J. Org. Chem.*, **22**, 455 (1957).
[22] Kornblum, Blackwood, and Mooberry, *J. Am. Chem. Soc.*, **78**, 1501 (1956).

primary and secondary nitroparaffins.[21] In contrast, alkyl chlorides react too slowly to be useful.

$$CH_3(CH_2)_5Br + NaNO_2 \xrightarrow{DMF} CH_3(CH_2)_5NO_2 \quad (60\%)$$

$$CH_3(CH_2)_5I + NaNO_2 \xrightarrow{DMF} CH_3(CH_2)_5NO_2 \quad (61\%)$$

$$\begin{array}{c}CH_2\\ \overset{|}{CH_2}\ \ CHBr\\ \overset{|}{CH_2{-}CH_2}\end{array} + NaNO_2 \xrightarrow{DMSO} \begin{array}{c}CH_2\\ \overset{|}{CH_2}\ \ CHNO_2\\ \overset{|}{CH_2{-}CH_2}\end{array} \quad (58\%)$$

$$CH_3(CH_2)_3CHICH_3 + NaNO_2 \xrightarrow{DMSO} CH_3(CH_2)_3CH(NO_2)CH_3 \quad (60\%)$$

$$C_6H_5CH_2Br + NaNO_2 \xrightarrow{DMF} C_6H_5CH_2NO_2 \quad (55\%)$$

$$p\text{-}O_2NC_6H_4CH_2Br + NaNO_2 \xrightarrow{DMF} p\text{-}O_2NC_6H_4CH_2NO_2 \quad (22\%)$$
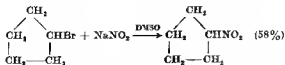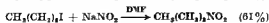
It is noteworthy that the yield of nitro compound obtained from benzyl bromide is slightly, but unmistakably, lower than that obtained from strictly aliphatic primary bromides while the yield from p-nitrobenzyl bromide is much lower   Undoubtedly related is the difficulty experienced in obtaining a pure product from the halide III.[24] The generalized significance of these results is discussed in the section dealing with the preparation of α-nitro esters (p. 113).

$$(3)$$
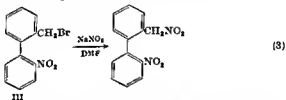
The reaction of sodium nitrite with t-butyl bromide, t-butyl chloride, cyclohexyl bromide, and cyclohexyl iodide fails to give nitro compounds; instead isobutylene and cyclohexene are obtained.[21] The recent report
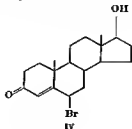
²⁴ Muth, Ellers, and Folmer, J Am Chem Soc, 79, 6501 (1957)

that 6β-bromotestosterone IV does not yield a nitro steroid on treatment with sodium nitrite in DMF[25] is not surprising. It is of interest that bromocycloheptane and iodocycloheptane give 55% and 58% yields, respectively, of nitrocycloheptane.[21]

Sulfonate esters may also be employed in the sodium nitrite reaction. Without any attempt to establish optimum conditions, n-octyl tosylate and n-butyl methanesulfonate were converted to the corresponding nitroparaffins in 43–46% yields.[21] The use of sulfonates would, of course, be advantageous when dealing with alcohols that rearrange on conversion into halides. In this connection it should be recalled that the conversion of secondary alcohols to the corresponding bromides, using hydrobromic acid or phosphorus tribromide, produces significant amounts of isomeric secondary bromides; e.g., from 2-pentanol between 10% and 28% of the product is 3-bromopentane.[26]

α-Nitro Esters. The reaction of α-halo esters with sodium nitrite is the only general method for preparing α-nitro esters. A wide variety of α-nitro esters can be prepared readily by this reaction in excellent yields.[27, 28] Some typical examples are given below.

$$CH_3CH_2CH_2CH(Br)CO_2C_2H_5 \xrightarrow[DMSO]{NaNO_2} CH_3CH_2CH_2CH(NO_2)CO_2C_2H_5 \quad (87\%)$$

$$C_6H_5CH(Br)CO_2C_2H_5 \xrightarrow[DMF]{NaNO_2} C_6H_5CH(NO_2)CO_2C_2H_5 \quad (70\%)$$
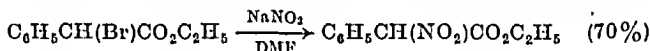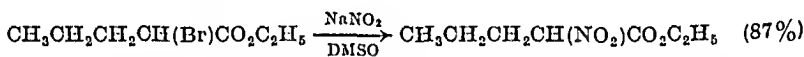
The preparation of ethyl α-nitroisobutyrate in 78–91% yield (equation 4) is of interest since t-alkyl halides give olefins on treatment with sodium nitrite. Also noteworthy is the fact that ethyl α-chloropropionate gives the same yield (68%) of ethyl α-nitropropionate as does the α-bromo ester.[28]

$$(CH_3)_2C(Br)CO_2C_2H_5 \xrightarrow{NaNO_2} (CH_3)_2C(NO_2)CO_2C_2H_5 \quad (78\text{–}91\%) \quad (4)$$
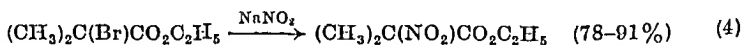
In only one instance does this new α-nitro ester synthesis fail. If ethyl bromoacetate is treated with sodium nitrite, a very rapid reaction occurs

$$C_2H_5O_2CC\text{———}CCO_2C_2H_5$$

V
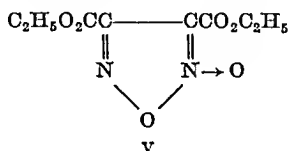
[25] Bowers, Sánchez, and Ringold, *J. Am. Chem. Soc.*, **81**, 3702 (1959).

[26] Pines, Rudin, and Ipatieff, *J. Am. Chem. Soc.*, **74**, 4063 (1952).

[27] Kornblum and Blackwood, *Org. Syntheses*, **37**, 44 (1957).

[28] Kornblum, Blackwood, and Powers, *J. Am. Chem. Soc.*, **79**, 2507 (1957).

but no ethyl nitroacetate can be isolated[15] Instead, depending on the temperature, oxalic acid or the furoxane V is produced.[15]

The failure to isolate any ethyl nitroacetate, the diminished yields noted above in reactions employing benzyl bromide and p-nitrobenzyl bromide, and the recently reported inability to obtain any 21-nitroprogesterone from the reaction of 21-iodoprogesterone VI with sodium nitrite in DMF[19] are apparently typical of what is to be anticipated when sodium

VI
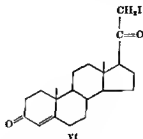
nitrite reacts with primary halides of the type A—CH₂—Halogen, where A is a powerful electron-withdrawing group Such compounds react rapidly with sodium nitrite in DMF (or DMSO) but give little, if any, of the corresponding primary nitro compound The reason is that nitro compounds of the type A—CH₂NO₂ are distinctly more acidic than simple aliphatic nitro compounds and they are *primary* nitro compounds, two facts which result in their unusually rapid destruction by the joint action of sodium nitrite and the nitrite ester concomitantly formed. A full discussion of this destructive process has been given.[15] Fortunately, it is with just such halides, e.g. ethyl iodoacetate and p-nitrobenzyl bromide, that the reaction with silver nitrite works especially well[14,15] (p. 107).

Miscellaneous Examples. The reaction of β-halogenated ketones with sodium nitrite in DMF has afforded the corresponding β-nitro ketones.[20]

$$CH_3CH_2COCH_2CH_2Cl + NaNO_2 \xrightarrow{DMF} CH_3CH_2COCH_2CH_2NO_2 \quad (48\%)$$

$$C_6H_5COCH_2CH_2Br + NaNO_2 \xrightarrow{DMF} C_6H_5COCH_2CH_2NO_2 \quad (37\%)$$
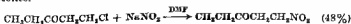
Treatment of α-bromoisobutyronitrile with sodium nitrite in DMF gives the nitro compound in 52% yield.[19]

$$(CH_3)_2C(Br)CN + NaNO_2 \xrightarrow{DMF} (CH_3)_2C(NO_2)CN$$
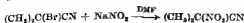
[19] Bowers and Ringold, *J Am Chem Soc.*, 81, 3711 (1959).
[20] Fusco and Rossi, *Chem & Ind (London)*, 1957, 1650

Although the report[31] that 2-nitroethanol ean be prepared by bubbling ethylene oxide into aqueous barium nitrite eould not be eonfirmed,[32,33] the reaetion of diisopropylammonium nitrite with eyelohexene oxide in DMSO gives a 23% yield of *trans*-2-nitrocyelohexanol.[33] Sinee the reaetion in DMSO was only examined briefly, it is quite possible that the yield eould be materially improved.

Preliminary studies indieate that the reaetion of sodium nitrite with α-bromo nitro eompounds may be useful for the preparation of *gem*-dinitro eompounds.[34]   Thus

$$
\begin{array}{c}
\text{CH}_2 \\
\diagup \quad \diagdown \\
\text{CH}_2 \qquad \text{CH}_2 \\
| \qquad\qquad | \\
\text{CH}_2\text{---CNO}_2 \\
| \\
\text{Br}
\end{array}
+ \text{NaNO}_2 \xrightarrow{\text{DMF}}
\begin{array}{c}
\text{CH}_2 \\
\diagup \quad \diagdown \\
\text{CH}_2 \qquad \text{CH}_2 \\
| \qquad\qquad | \\
\text{CH}_2\text{---C(NO}_2)_2
\end{array}
\quad (28\%)
$$

$$(CH_3)_2C(NO_2)Br + NaNO_2 \xrightarrow{\text{DMF}} (CH_3)_2C(NO_2)_2 \quad (45\%)$$
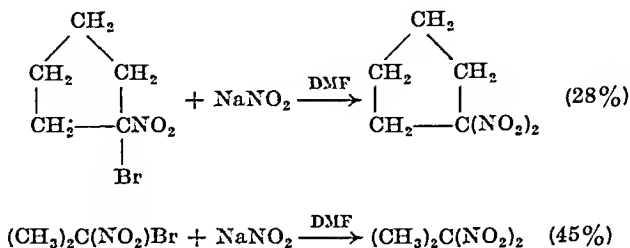
The Relative Value of Silver Nitrite and Sodium Nitrite for the Synthesis of Particular Types of Nitro Compounds

In the synthesis of saturated primary nitro compounds, silver nitrite gives nitroparaffins in about 80% yields as against about 60% yields obtained with sodium nitrite.   While silver nitrite is, therefore, the reagent of ehoiee here, the lower eost and ready availability of sodium nitrite, the not very large disparity in yield, and the shorter reaetion time all combine to make sodium nitrite an exeellent second ehoiee.   If, however, the primary nitro compound is of the type $A\text{---CH}_2\text{NO}_2$, where A is carbethoxy, *p*-nitrophenyl, or some other powerful electron-with-drawing group, silver nitrite is greatly preferred.

Sodium nitrite is far superior to silver nitrite for the synthesis of *all types* of secondary nitro compounds.

Experimental Conditions

The reaction of alkyl halides with sodium nitrite is generally carried out at room temperature; with benzylic halides a temperature in the neighborhood of −20° is employed.   Since DMSO freezes at 18°, it

[31] S. Miura, Jap. pat. 156,256 (1943) [*C.A.*, **44**, 2008 (1950)].
[32] Noland, Freeman, and Baker, *J. Am. Chem. Soc.*, **78**, 188 (1956).
[33] Stevens and Emmons, *J. Am. Chem. Soc.*, **79**, 6014 (1957).
[34] J. W. Powers, Ph.D. Thesis, Purdue University, 1957.

cannot be employed at low temperatures; the importance of this restriction may be appreciated from the results obtained on converting α-phenylethyl bromide to the nitro compound. In DMF at −16° a 43% yield of pure product is isolated, whereas in DMSO at 11° the yield is only 22%.[25]

In general, DMF and DMSO are about equally useful as solvents. It should be remembered, however, that DMSO is not a completely inert solvent. For example, it has been found that, at room temperature, DMSO oxidizes phenacyl bromides to the corresponding glyoxals.[26]

$$C_6H_5COCH_2Br \xrightarrow{DMSO} C_6H_5COCHO$$
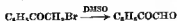
In the synthesis of nitro compounds from α-halo esters, secondary bromides, and alicyclic iodides, phloroglucinol is added to prevent the nitrosation process from destroying the nitro compound With phloroglucinol present excessive reaction time is no longer critical, the only requirement being that sufficient time be given for the halide to react completely.

When phloroglucinol is not employed it is necessary to work up the reaction mixture promptly to prevent nitrosation. In DMF, primary bromides need a reaction time of 6 hours and primary iodides require 2½ hours, the addition of urea, by solubilizing the sodium nitrite, halves the reaction time. Because sodium nitrite is considerably more soluble in DMSO than in DMF, much more concentrated solutions can be prepared and this makes possible shorter reaction times Reference should be made to the original papers[21,22] for further details concerning reaction times. A convenient means of following the reaction is to titrate the liberated halide ion.

Lithium and potassium nitrites are as effective as sodium nitrite, the preference for sodium nitrite is based on price and availability

THE OXIDATION OF AMINES

Although tertiary nitroparaffins have been known for many years, they have never been obtained by reactions which could be regarded as synthetically useful. Thus liquid phase nitration generally involves heating small amounts of a hydrocarbon in sealed tubes with dilute nitric acid to 130–150° for prolonged periods. A large number of tubes are required, and they need to be opened for periodic relief of pressure, complex mixtures are produced, and the yields of pure tertiary nitro compounds are poor.[27]

[25] N Kornblum and W D Gurowitz, Unpublished work

[26] Kornblum, Powers, Anderson, Jones, Larson. Levand, and Weaver, J Am Chem Soc. 79, 6562 (1957), Kornblum, Jones, and Anderson, ibid, 81, 4113 (1959)

[27] See, e g , Nametkin and Zabrodina, Doklady Akad Nauk S.S.S R , 75, 395 (1950) [C.A , 45, 6998 (1951)]

The vapor phase nitration process devised by Hass, Hodge, and Vanderbilt,[38] despite its commercial importance, can hardly be regarded as a laboratory synthesis, the more so because it gives rise to complex mixtures. Finally, the classical reaction of silver nitrite with alkyl halides is worthless for the preparation of tertiary nitroparaffins.[10]

A simple and reliable procedure for oxidizing tertiary carbinamines, $RR'R''CNH_2$, to the corresponding tertiary nitro compounds at 25–30° has recently been devised.[39] This procedure, which employs potassium permanganate, has the virtue of being applicable, without alteration, to a wide variety of amines; furthermore, it gives excellent yields of pure tertiary nitroparaffins. The method also has the advantage of starting with tertiary carbinamines, substances which have become easily accessible.[40]

The permanganate oxidation of t-butylamine in aqueous solution gives the tertiary nitrobutane in 83% yield. Amines of higher molecular weight which are insoluble in water are dissolved in a mixture of 80%

$$(CH_3)_3CNH_2 \rightarrow (CH_3)_3CNO_2$$
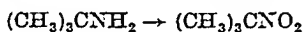
acetone and 20% water, and the pH is controlled by adding magnesium sulfate. A typical example is the synthesis of the tertiary nitroöctane VII in 77% yield.[39]

$$\underset{NH_2}{(CH_3)_3CCH_2C(CH_3)_2} \rightarrow \underset{\underset{VII}{NO_2}}{(CH_3)_3CCH_2C(CH_3)_2}$$
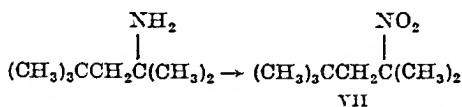
Primary amines of the type RCH_2NH_2 or R_2CHNH_2 have not been tried in reaction with potassium permanganate, although it is presumed they will not give nitro compounds. The ability of a primary amine to be oxidized by permanganate to a nitro compound (which was reduced back to the original amine) has been used as a diagnostic for the t-carbinamine structure, $RR'R''CNH_2$.[13]

In only one instance does the permanganate oxidation fail to give the desired t-nitro compound. When oxidation of triphenylmethylamine to triphenylnitromethane is attempted the only product isolated, aside from a 40% recovery of the amine, is triphenylcarbinol (33% yield based on the amine which reacted). This failure could have been anticipated from the report that triphenylnitromethane is readily decomposed by moisture.[41]

[38] Hass, Hodge, and Vanderbilt, *Ind. Eng. Chem.*, **28**, 339 (1936).
[39] Kornblum, Clutter, and W. J. Jones, *J. Am. Chem. Soc.*, **78**, 4003 (1956).
[40] Ritter and Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948).
[41] Schlenk, Mair, and Bornhardt, *Ber.*, **44**, 1173 (1911).

Emmons[41] has briefly examined the oxidation of aliphatic amines with peracetic acid Although the oxidation of t-octylamine gives an 87% yield of the tertiary nitrooctane VII, Emmons regards the permanganate oxidation of t-carbinamines to tertiary nitro compounds as a more convenient preparation

It is significant that peracetic acid can be employed for the synthesis of secondary nitroparaffins Thus nitrocyclohexane is obtained in 70% yield on oxidizing cyclohexylamine, while 2-nitrobutane is isolated in 65% yield from 2-aminobutane Although these were the only amines studied, oxidation with peracetic acid appears very much worth considering for the preparation of secondary nitro compounds Indeed, except for the oxidation of oximes (p. 119), this is the only laboratory method available for introducing a nitro group into the cyclohexane nucleus

The preparation of only one primary nitro compound by the use of peracetic acid is reported n-Hexylamine gives 1-nitrohexane in 33% yield.[42]

Attempts to oxidize aliphatic amines with trifluoroperacetic acid lead to the formation of the amine trifluoroacetate salts Solutions of trifluoroacetic acid always contain considerable quantities of trifluoroacetic acid, as this is a strong enough acid to protonate virtually all the amine, the oxidation does not take place When a sodium carbonate buffer system is present it is possible to obtain a reaction between an aliphatic amine and trifluoroperacetic acid, but the product is the N-alkyl trifluoroacetamide[43]

$$RCH_2NH_2 + CF_3CO_2OH \rightarrow RCH_2NHCOCF_3 + H_2O_2$$
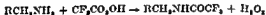
In a preliminary experiment t-butylamine was converted to 2-nitro-2-methylpropane in 31% yield by treatment with alkaline hydrogen peroxide[39] Since hydrogen peroxide offers no advantage in the laboratory, its use has not been investigated further.

THE OXIDATION OF OXIMES

Two principal methods are available for oxidizing oximes to nitro compounds. One, developed by Emmons[43] uses peroxytrifluoroacetic acid as the oxidant The other, developed by Iffland,[44-46] involves three

[41] Emmons, J Am Chem Soc , 79, 5528 (1957)

[42] Emmons and Pagano, J Am Chem Soc , 77, 4557 (1955)

[43] Iffland and Criner, J Am Chem Soc , 75, 4047 (1953)

[44] Iffland, Criner, Koral, Lotspeich, Papanastassiou, and White, J Am Chem Soc , 75, 4044 (1953)

[45] Iffland and Yen, J Am Chem Soc , 76, 4083 (1954)

a buffer is added. Sodium bicarbonate is a satisfactory buffer in the oxidation of aliphatic oximes, while disodium hydrogen phosphate is used with aromatic and alicyclic oximes. The addition of small amounts of urea for scavenging any nitrogen oxides increases the yields significantly. Oxidation normally is carried out by the slow addition of an anhydrous solution of peroxytrifluoroacetic acid in acetonitrile to an acetonitrile solution of the oxime in which the buffer is slurried. Gentle reflux is maintained throughout the addition; too rapid addition of the peracid or overheating lowers the yield of nitroparaffin markedly. Some typical results are shown in the accompanying equations.

$$CH_3(CH_2)_5CH{=}NOH \rightarrow CH_3(CH_2)_5NO_2 \quad (72\%)$$

$$C_6H_5CH{=}NOH \rightarrow C_6H_5CH_2NO_2 \quad (77\%)$$

$$
\begin{array}{ccc}
\quad CH_2 & & CH_2 \\
CH_2 \quad CH_2 & & CH_2 \quad CH_2 \\
| \qquad | & \rightarrow & | \qquad | \qquad (62\%) \\
CH_2 \quad CH_2 & & CH_2 \quad CH_2 \\
\;\; C{=}NOH & & \;\; CHNO_2 \\
\quad CH_2 & & CH_2
\end{array}
$$

$$(CH_3CH_2CH_2)_2C{=}NOH \rightarrow (CH_3CH_2CH_2)_2CHNO_2 \quad (64\%)$$

$$CH_3CH_2CH_2(CH_3)_2C{=}NOH \rightarrow CH_3CH_2CH(CH_3)_2CHNO_2 \quad (43\%)$$

$$C_6H_5C(CH_3){=}NOH \rightarrow C_6H_5CH(CH_3)NO_2 \quad (69\%)$$
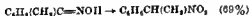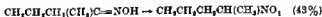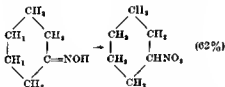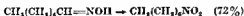
The preparation of nitrocyclohexane is especially noteworthy, for neither the sodium nitrite nor the silver nitrite reaction with cyclohexyl halides gives nitro compounds. Aside from the Iffland method of oxidizing oximes (which gives a 50% yield of nitrocyclohexane), the only other example of a laboratory procedure for the introduction of a nitro group into a cyclohexane nucleus is the peracetic acid oxidation of cyclohexyl-amine,[42] which gives a 70% yield of nitrocyclohexane (see p. 117). But, more often than not, the requisite amine would be obtained by reduction of the oxime.

The preparation of α-phenylnitroethane in 69% yield suggests that the Emmons-Pagano peroxytrifluoroacetic acid oxidation procedure may prove especially valuable for the synthesis of nitro compounds such as ArCH(R)NO₂.

The peroxytrifluoroacetic acid oxidation of oximes is rather sensitive to steric hindrance. Neither pinacolone oxime nor trimethylacetaldehyde oxime is oxidized successfully by this procedure. In both cases most of the oxime is recovered. In contrast, Iffland and Yen[45] have converted

pinacolone oxime to the pure nitro compound VIII in 36% yield by the three-step procedure. It is unlikely that any other method of preparing nitroparaffins would be a practical route to this compound.

$$(CH_3)_3CC\!\!=\!\!NOH \rightarrow (CH_3)_3CCHNO_2$$
$$\underset{CH_3}{|} \qquad\qquad \underset{\underset{VIII}{CH_3}}{|}$$
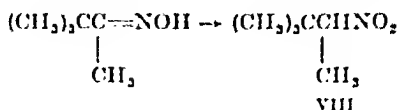
In the three-step sequence the oxime is first treated with either N-bromosuccinimide or N-bromoacetamide, and the resulting bromo nitroso compound is then oxidized to the bromo nitro compound by a mixture of nitric acid and 30% hydrogen peroxide. The bromo nitro compound is debrominated with sodium borohydride. It is not necessary to isolate or purify any of the intermediates. The procedure can be used only for the synthesis of nitrocycloalkanes and secondary nitroalkanes; it fails completely with aldoximes and aromatic ketoximes. As noted earlier, cyclohexanone oxime gives nitrocyclohexane in 50% yield; this and the 55% yield obtained in preparing nitrocyclopentane are the best yields which have been obtained. The accompanying equations illustrate some more typical results.

$$\begin{array}{cc} CH_2\!\!-\!\!C\!\!=\!\!NOH & CH_2\!\!-\!\!CHNO_2 \\ |\qquad | & |\qquad | \\ CH_2\!\!-\!\!CH_2 & CH_2\!\!-\!\!CH_2 \end{array} \quad (23\%)$$

$$(CH_3CH_2CH_2)_2C\!\!=\!\!NOH \rightarrow (CH_3CH_2CH_2)_2CHNO_2 \quad (28\%)$$
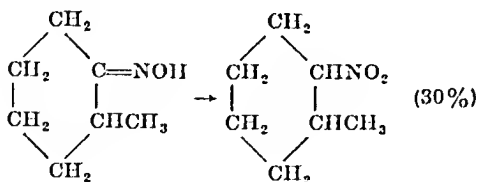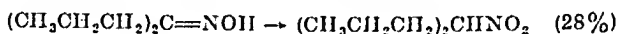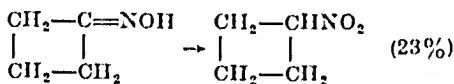
THE REACTION OF ACTIVE METHYLENE COMPOUNDS WITH NITRATE ESTERS

The nitration of an active methylene compound by the action of a nitrate ester under basic conditions has found some use in synthesis. Indeed, the preparation of phenylnitromethane described in *Organic Syntheses*[49] employs this reaction and provides phenylnitromethane in an over-all yield of 50–55%.

[49] Black and Babers, *Org. Syntheses*, *Coll. Vol.* **2**, 512 (1943).

$$C_6H_5CH_2CN + CH_3ONO_2 \xrightarrow{C_2H_5ONa} C_6H_5C=NO_2Na \xrightarrow{NaOH}$$
$$\underset{CN}{\overset{}{|}}$$

$$C_6H_5C=NO_2Na \xrightarrow{HC} CO_2 + C_6H_5CH_2NO_2$$
$$\underset{CO_2Na}{\overset{}{|}}$$
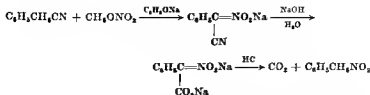
Early in the present century Wislicenus and his students showed that arylacetonitriles such as *p*-bromophenylacetonitrile,[50] arylacetic esters,[51]

$$p\text{-}BrC_6H_4CH_2CN \xrightarrow[C_2H_5ONO_2]{C_2H_5ONa} p\text{-}BrC_6H_4C=NO_2Na \quad (85\text{--}90\%)$$
$$\underset{CN}{\overset{}{|}}$$
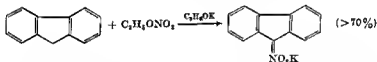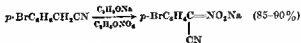
and fluorene[52] could be nitrated with ethyl nitrate, often in excellent yields. A distinguishing feature of the reaction with arylacetic esters is the loss of the ester group as diethyl carbonate. Thus, from the ethyl ester of phenylacetic acid, the product is the salt of phenylnitromethane[51]

$$C_6H_5CH_2CO_2C_2H_5 \xrightarrow[C_2H_5ONO_2]{C_2H_5OK} C_6H_5CH=NO_2K + (C_2H_5O)_2CO$$
$$(60\%)$$
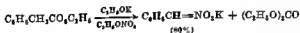
It is difficult to evaluate this method Yields, when reported, are usually based on the crude salt of the nitro compound Nitro salts are, in general, not easy to purify, and those derived from nitrated active methylene compounds are even more likely to be labile and difficult to purify. In addition, many of these salts are hygroscopic. The generation of the nitro compound from its salt by acidification involves the risk that some decomposition to the corresponding aldehyde or ketone (the Nef reaction) may take place.[53] And, finally, the nitro compounds derived from active methylene compounds are often intrinsically unstable [54–56]

Bromination of the nitro salts has been employed as a device for

[50] Wislicenus and Elvert, *Ber.* **41**, 4121 (1908)

[51] Wislicenus and Grützner, *Ber.* **42**, 1930 (1909)

[52] Wislicenus and Waldmueller, *Ber.* **41**, 3335 (1908)

[53] Kornblum and Graham, *J. Am Chem Soc*, **73**, 4041 (1951)

[54] Wieland, Garbsch, and Chavan, *Ann.*, **461**, 295 (1928)

[55] Feuer, Shepherd, and Savides, *J. Am Chem Soc*, **78**, 4364 (1956)

[56] Feuer and Savides, *J Am Chem Soc.* **81**, 5826 (1959)

identifying the nitration products and, since bromination of nitro salts is virtually a quantitative process, for determining yields.[55–58] Thus with adiponitrile the over-all yield of α,α'-dibromo-α,α'-dinitroadiponitrile is 79%, while with hexanenitrile a 55% yield of the corresponding bromonitronitrile is isolated.[56] Lower limits for the yields of the corresponding nitronitrile salts are thereby established.

$$NCCH_2CH_2CH_2CH_2CN \xrightarrow[\text{(CH}_3\text{)}_3\text{COK}]{\text{Amyl nitrate}} \left[\overset{NO_2}{\underset{\parallel}{N}}CC\overset{NO_2}{\underset{\parallel}{C}}H_2CH_2\overset{}{C}CN \right]^{=} 2K^+ \xrightarrow{\text{Br}_2}$$

$$NC\overset{NO_2}{\underset{Br}{C}}CCH_2CH_2\overset{NO_2}{\underset{Br}{C}}CN$$

$$CH_3(CH_2)_4CN \xrightarrow[\text{(CH}_3\text{)}_3\text{COK}]{\text{Amyl nitrate}} \left[CH_3(CH_2)_3\overset{}{C}CN \atop \underset{NO_2}{\parallel} \right]^{-} K^+ \xrightarrow{\text{Br}_2}$$

$$CH_3(CH_2)_3CBrNO_2CN$$
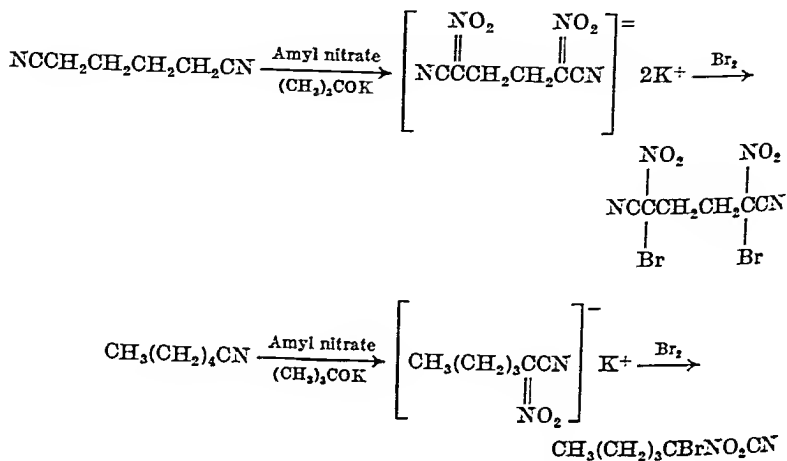
It was realized early that not all bases are equally useful in these reactions. In particular, it was recognized that potassium ethoxide is superior to sodium ethoxide in effecting nitrations. For example, o-bromophenylacetonitrile is nitrated by ethyl nitrate in the presence of sodium ethoxide to give the sodium salt of o-bromophenylnitroacetonitrile in 30% yield, whereas with potassium ethoxide the yield of the salt is 70%.[59] While fluorene gives a 70% yield of the potassium salt of 9-nitrofluorene when potassium ethoxide is employed as the base, with sodium ethoxide no nitration occurs.[52]

Recent studies of the nitration of aliphatic nitriles,[56] ketones,[56] dinitriles,[56] and cyclic ketones[55] have dealt with the usefulness of various bases in these condensations, and with the influence of solvent, temperature, reaction time, and mode of addition. It has been found that sublimed potassium t-butoxide in tetrahydrofuran is the best reagent. The following equations are illustrative.[55,56] The reaction with cyclopentanone is particularly interesting. Ring opening on

[57] K. Klager, personal communication to Henry Feuer; cf. Doctoral Dissertation of J. W. Shepherd, Purdue University, 1954, pp. 7–8.

[58] Klager, *J. Org. Chem.*, 20, 646 (1955).

[59] Wislicenus and M. Fischer, *Ber.*, 43, 2235 (1910).

$$(CH_3CH_2CH_2)CO \xrightarrow[\text{(CH}_3)_3COK]{\text{Amyl nitrate}} \left(CH_3CH_2C{-\atop NO_2K} \right)_2 CO \xrightarrow{Br_2}$$

$$\left(CH_3CH_2CBr{\atop NO_2} \right)_2 CO \quad \text{(ca. 50\%)}$$

$$O_2NCBrCH_2CH_2CBr_2NO_2 + K_2CO_3 \quad (54\%)$$
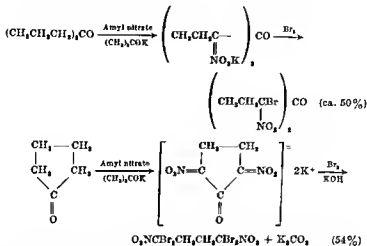
bromination[58] has been shown to be a general reaction of the salts of α,α'-dinitrocycloalkanones.[58] Presumably the dibromodinitrocyclo-pentanone is an intermediate and reacts with hydroxide ion.
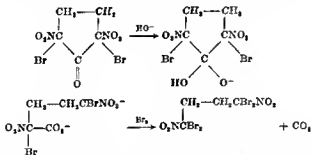
Nitration by a nitrate ester can be intramolecular. The 1,3-nitronitrate IX readily rearranges to the dinitro alcohol X in aqueous ethanolic potassium hydroxide.[60]
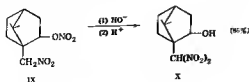
60 T. E. Stevens, J. Org Chem., 24, 865 [1959]

Nitration by nitrate esters involves, in essence, nucleophilic displacement by the carbanion being nitrated on the nitrogen of the nitrate ester (equation 5).   But the alternative process of nucleophilic displacement on

$$A:^- + RONO_2 \rightarrow ANO_2 + RO^- \tag{5}$$
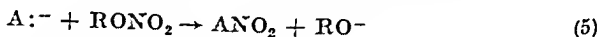
carbon is known; and, with the relatively weakly basic anions derived from malonic and acetoacetic esters, it is the latter mode of reaction which is observed (equations 6 and 7).[61]

$$[CH(CO_2C_2H_5)_2]^- + C_6H_5CH_2ONO_2 \rightarrow C_6H_5CH_2CH(CO_2C_2H_5)_2 + NO_3^- \tag{6}$$

$$[CH_3COCHCO_2C_2H_5]^- + C_6H_5CH_2ONO_2 \rightarrow CH_3COCHCO_2C_2H_5 + NO_3^- \tag{7}$$
$$\underset{CH_2C_6H_5}{|}$$
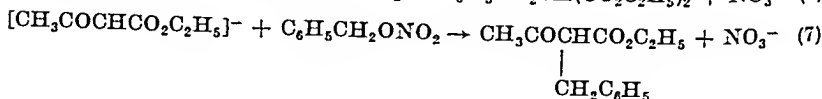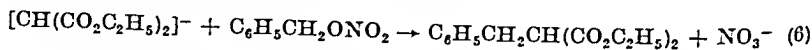
Nitration, rather than alkylation, of the anions of malonic and acetoacetic esters can be achieved by the use of acetone cyanohydrin nitrate.[62]

$$[CH(CO_2C_2H_5)_2]^- + (CH_3)_2CONO_2 \rightarrow CH(CO_2C_2H_5)_2 + (CH_3)_2CO + CN^-$$
$$\underset{CN}{|} \qquad \underset{NO_2}{|}$$
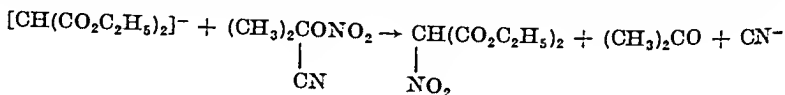
Since nitromalonic ester is a distinctly stronger acid than malonic ester, a second mole of base is needed to prevent destruction of an equivalent of sodiomalonic ester.   But an excess of the base (sodium hydride)

$$H:^- + CH(CO_2C_2H_5)_2 \rightarrow HCO_2C_2H_5 + [O_2NCHCO_2C_2H_5]^- \tag{8}$$
$$\underset{NO_2}{|}$$
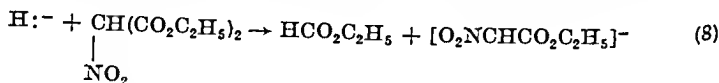
cannot be used as it degrades the nitromalonic ester to ethyl nitroacetate (equation 8); therefore an excess of sodiomalonic ester is employed. With a three-fold excess of sodiomalonic ester, diethyl nitromalonate is obtained in 45% yield.   As a means of preparing nitromalonic ester, nitration with acetone cyanohydrin nitrate is inferior to the nitration of malonic ester with nitric acid, which consistently gives yields of over 90%[63] (see p. 136).

Nitration of monosubstituted malonic or acetoacetic esters with acetone cyanohydrin nitrate, in the presence of a 100% excess of sodium hydride, results in degradation to α-nitro esters analogous to that described by equation 8 and constitutes a general synthesis of α-nitro esters (equation 9).[62]   The yields average 50–55% and are comparable from either type of ester.   While this method will doubtless be useful in particular instances,

[61] Nef, *Ann.*, **309**, 172 (1899).
[62] Emmons and Freeman, *J. Am. Chem. Soc.*, **77**, 4391, 4673 (1955).
[63] Weisblat and Lyttle, *J. Am. Chem. Soc.*, **71**, 3080 (1949).

$$RCH(CO_2C_2H_5)_2$$
or
$$\begin{array}{c} RCHCO_2C_2H_5 \\ | \\ COCH_3 \end{array} + (CH_3)_2CONO_2 \xrightarrow{2NaOH} \begin{array}{c} RCHCO_2C_2H_5 \\ | \\ NO_2 \end{array} \qquad (9)$$
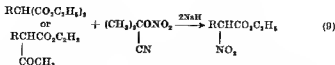
it is greatly inferior to the general synthesis of α-nitro esters which employs α-halo esters and sodium nitrite (p 112) [27,28]

Acetone cyanohydrin nitrate is rapidly destroyed by metal alkoxides and, presumably, the same type of destructive process is responsible for the failure to nitrate the anions of such compounds as t-butyl acetate, acetophenone, and diethyl succinate.[44] Acetone cyanohydrin nitrate is thus of limited utility for nitrating carbanions.

Self-condensation of the active methylene compound, which may become an important side reaction, can be minimized by completely converting the active methylene compound to its salt. For this purpose the strong base potassium t-butoxide and the non-protic solvent tetrahydrofuran serve very well [45]

Nitrate esters are attacked by bases and, indeed, three reaction types are known. By way of illustration the reactions involving hydroxide ion are given [46] These, presumably, are to a greater or lesser extent a

$$HO^- + RONO_2 \rightarrow HOR + NO_3^-$$
$$HO^- + RCH_2CH_2ONO_2 \rightarrow RCH=CH_2 + H_2O + NO_3^-$$
$$HO^- + RCH_2ONO_2 \rightarrow RCHO + H_2O + NO_2^-$$
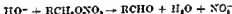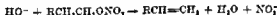
source of difficulty in carrying out nitrations by nitrate esters under basic conditions.

THE REACTION OF ACTIVE METHYLENE COMPOUNDS WITH NITRIC ACID OR OXIDES OF NITROGEN

Whereas the direct nitration of hydrocarbons with nitric acid or oxides of nitrogen is, at best, inconvenient for the preparation of pure compounds in the laboratory, high yields of pure products can be obtained from active methylene compounds under rather mild conditions. When diethyl malonate is treated with fuming nitric acid for several hours at 15-20°, diethyl nitromalonate is consistently obtained in about 92% yields [62,63]

$$H_2C(CO_2C_2H_5)_2 \xrightarrow{HNO_3} O_2NCH(CO_2C_2H_5)_2$$
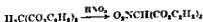
It is important to recognize that the nitro ester thus prepared is invariably contaminated by oxides of nitrogen which initiate autocatalytic decomposition of the nitro ester. These oxides, which cannot be removed by

[44] Bachman, Morrow and Van Dolah, Chem Rev. 55, 491 (1955)
[45] Arndt and Rose J Chem Soc. 1935, 1

repeated washing and/or distillation, are completely removed by treatment with urea or acetamide. Diethyl nitromalonate so treated is stable over long periods of time.[63]

The nitration of indane-1,3-dione occurs readily at 40° on treatment with 90% nitric acid in acetic acid.[66]

(67%)
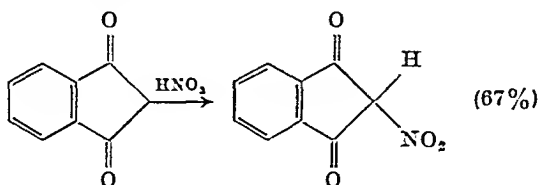
The facility with which 1,3-indanediones can be nitrated has been employed in an ingenious manner by Zalukaev and Vanag for the synthesis of primary nitro compounds.[67] The 1,3-indanediones on which this
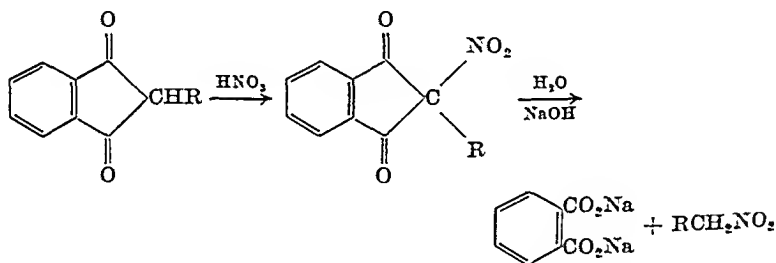
synthesis is based are readily available, especially those in which R is a heterocyclic or aromatic nucleus. With R = α-naphthyl, the nitration step occurs in 52–60% yield and hydrolysis by 5% aqueous sodium hydroxide gives pure α-naphthylnitromethane in 57% yield. While α-naphthylnitromethane can almost certainly be prepared more conveniently by a number of other methods, the Zalukaev procedure may well prove successful where other methods are inapplicable. For example, it is quite possible that nitroneopentane, $(CH_3)_3CCH_2NO_2$, can be prepared via an indanedione.

α,α-Dinitro esters can be obtained, although in poor yield, by nitration of half esters of malonic acids with 70% nitric acid.[68] In this way the

$$RCH(CO_2H)CO_2C_2H_5 \xrightarrow{HNO_3} RC(NO_2)_2CO_2C_2H_5$$
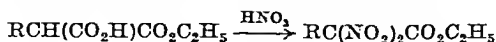
[66] Fieser, *Experiments in Organic Chemistry*, 3rd ed., pp. 127–128, Heath, Boston, 1955; Wanag and Lode, *Ber.*, 71, 1267 (1938).

[67] Zalukaev and Vanag, *J. Gen. Chem. (U.S.S.R.)*, 26, 657 (1956). (English Translation by Consultants Bureau, New York, N.Y.)

[68] Kissinger and Ungnade, *J. Org. Chem.*, 23, 1340 (1958).

dinitro esters in which R = H, CH_3, C_2H_5, or $n\text{-}C_3H_7$ have been prepared in 8–17% yields.

Nitration with oxides of nitrogen has had only limited use. Diphenylcyanonitromethane has been prepared by treating a chloroform solution of diphenyleyanomethane with dry nitrogen dioxide at 15–20°.[88]

$$(C_6H_5)_2CHCN \xrightarrow{NO_2} (C_6H_5)_2C(CN)NO_2 \quad (57\%)$$

Diphenylnitromethane has been obtained from diphenylmethane and nitrogen dioxide at 70–75° in carbon tetrachloride solution with anhydrous copper sulfate and oxygen present.[70]

$$(C_6H_5)_2CH_2 \xrightarrow[\text{CuSO}_4]{O_2} (C_6H_5)_2CHNO_2 \quad (\text{ca. }50\%)$$
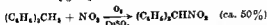
If oxygen is not available the reaction produces significant amounts of dinitrodiphenylmethane. The presence of oxygen is necessary to prevent build-up of the concentration of nitric oxide which, in conjunction with dinitrogen tetroxide, converts diphenylmethane to dinitrodiphenylmethane. The accompanying reaction scheme has been proposed to accommodate these facts.[70]

$$(C_6H_5)_2CH_2 + NO_2 \rightarrow (C_6H_5)_2\overset{\cdot}{C}H + HNO_2$$

$$(C_6H_5)_2\overset{\cdot}{C}H + NO_2 \rightarrow (C_6H_5)_2CHNO_2$$

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O$$

$$N_2O_3 \rightleftharpoons NO + NO_2$$

$$(C_6H_5)_2\overset{\cdot}{C}H + NO \rightarrow (C_6H_5)_2CHNO$$

$$(C_6H_5)_2CHNO + N_2O_4 \rightarrow (C_6H_5)_2C(NO_2)_2$$
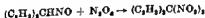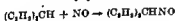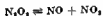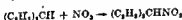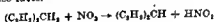
MISCELLANEOUS METHODS OF INTRODUCING A NITRO GROUP

This section briefly describes miscellaneous reactions of rather limited utility or reactions concerning which there are but few data.

Triphenylnitromethane has been obtained by the reaction of triphenylmethyl radicals with nitrogen dioxide in diethyl ether solution.[81]

$$(C_6H_5)_3C \cdot + NO_2 \rightarrow (C_6H_5)_3CNO_2 + (C_6H_5)_3CONO$$
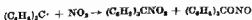
Ultraviolet irradiation of a gaseous mixture of a perfluoroalkyl iodide and nitric oxide in silica vessels, mercury being present to remove iodine, results in the replacement of iodine by a nitroso group. The yields are good. The nitroso compounds are oxidized by hydrogen peroxide to the corresponding nitro compounds.[71]

[68] Wittig and Pockels, *Ber.*, **69**, 790 (1936).
[70] Titov, *J. Gen. Chem. (U.S.S.R.)*, **18**, 1312 (1948) [*C.A.*, **43**, 4217 (1949)].
[71] Banus, *J. Chem. Soc.*, **1953**, 3755.

$$F_3CI \xrightarrow{hr} F_3C\cdot + I\cdot$$

$$F_3C\cdot + NO \longrightarrow F_3CNO \xrightarrow{H_2O_2} F_3CNO_2$$
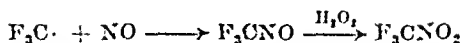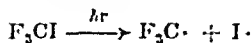
Addition of an olefin to a solution of pure nitrogen tetroxide in diethyl ether at 0° with oxygen present produces a mixture of the 1,2-dinitro compound, the nitroalkyl nitrate, and the nitroalkyl nitrite. Properly
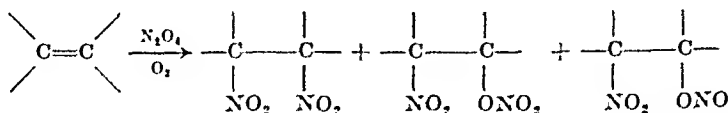
conducted, this can be a useful method for preparing 1,2-dinitro compounds.[12] Some typical nitro compounds obtained in this way are given below.

$O_2NCH_2CH_2NO_2$ (37%) $(CH_3)_3CCH_2C(CH_3)CH_2NO_2$ (53%)
                                                                  |
                                                                 NO_2
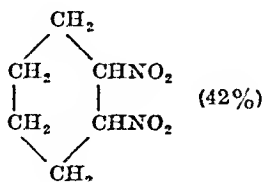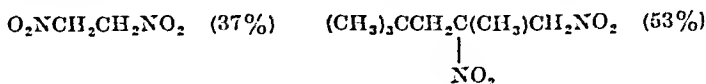
The nitration of unsaturated steroids is a useful reaction.[72] Thus,
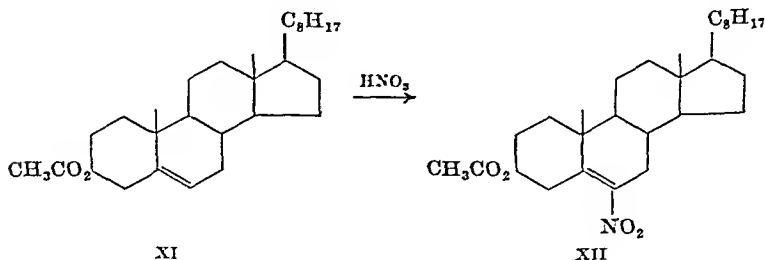
treatment of cholesteryl acetate XI in ether solution at 0° with fuming nitric acid affords pure 6-nitrocholesteryl acetate XII in 72% yield.[73] In the same way XIII is converted to XIV.[74] The importance of temperature control in these nitrations has been emphasized.[74]

[72] Fieser and Fieser, *Steroids*, pp. 43–44, Reinhold, New York, 1959.
[73] Anagnostopoulos and Fieser, *J. Am. Chem. Soc.*, **76**, 532 (1954).
[74] Bowers, Ibáñez, and Ringold, *J. Am. Chem. Soc.*, **81**, 3707 (1959).

$$XIII \qquad\qquad XIV$$
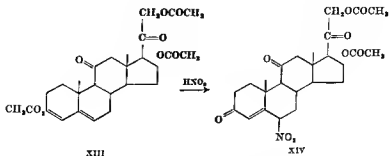
COMPARISON OF THE VARIOUS PROCEDURES FOR INTRODUCING A NITRO GROUP

Certain generalizations are possible regarding the effectiveness of the various procedures for the preparation of particular types of nitro compounds. These are noted in the table below.

Nitro Compounds	Preferred Procedures
Primary nitroparaffins	Silver nitrite + alkyl halide Sodium nitrite + alkyl halide Aldoxime + peroxytrifluoroacetic acid

Note: For the synthesis of ACH_2NO_2, where A is a powerful electron-withdrawing group, e.g., carbethoxy, *p*-nitrophenyl, the use of sodium nitrite is to be avoided.

Secondary nitroparaffins	Sodium nitrite + alkyl halide (or sulfonate ester) Amine + peracetic acid Ketoxime + peroxytrifluoroacetic acid Ketoxime + N-bromosuccinimide followed by sodium borohydride

Note: Sodium nitrite fails with cyclohexyl halides. Really pure secondary bromides are not likely to be obtained by the action of hydrobromic acid or phosphorus tribromide on secondary alcohols (p. 112). The ketoxime + N-bromosuccinimide procedure fails with aromatic ketoximes and is, in general, inferior to the peroxytrifluoroacetic acid method. However, in the oxidation of hindered oximes (where peroxytrifluoroacetic acid fails) the N-bromosuccinimide method is successful.

Tertiary nitroparaffins	Potassium permanganate + *t*-carbinamines Peracetic acid + *t*-carbinamines

α-Nitro esters	Sodium nitrite + α-halo esters
	Acetone cyanohydrin nitrate + sodium enolates of monosubstituted malonic or acetoacetic esters
	Silver nitrite + α-halo esters
	Note: Nitromalonic ester is best prepared by nitrating malonic ester with nitric acid.
α-Nitro nitriles	Nitrate ester + potassium *t*-butoxide + nitrile
	Sodium nitrite + α-halo nitrile
α-Nitro ketones	Nitrate ester + potassium *t*-butoxide + ketone
2-Nitro-1,3-diketones	Nitric acid + 1,3-diketone

EXPERIMENTAL PROCEDURES

Syntheses Employing Silver Nitrite

Silver Nitrite. The preparation of this salt is given in *Organic Syntheses*.[75]

1-Nitroöctane. Detailed directions for the synthesis of this nitro-paraffin in 75–80% yield from 1-bromoöctane are given in *Organic Syntheses*.[75]

1,4-Dinitrobutane. The preparation of this dinitro compound in 41–46% yield from 1,4-diiodobutane is given in *Organic Syntheses*.[9]

Phenylnitromethane.[8] A slurry of 100 g. of silver nitrite and 1 g. of calcium hydride in 250 ml. of anhydrous ether is cooled to 0° in a 500-ml. three-necked flask fitted with a dropping funnel, stirrer, and drying tube, and 85.5 g. (0.5 mole) of benzyl bromide (n_D^{20} 1.5762) is added dropwise to the stirred mixture over a period of 1 hour. After stirring at 0° in the dark for a total of 25 hours, tests for unreacted halide using a saturated solution of silver nitrate in acetonitrile and the Beilstein test are negative. The reaction mixture is filtered, the silver salts are washed with ether, and the washings are added to the original filtrate. About 1 g. of calcium hydride is added to the ether solution and the ether is distilled at atmospheric pressure through a 1 × 50 cm. glass helix packed column; the bath temperature is maintained between 48° and 50°. The last of the ether is removed under the vacuum of a water pump and the residual liquid is distilled through a 6-in. Vigreux column. Nineteen grams (28% yield) of benzyl nitrite is obtained, b.p. 56–56.5°/8 mm.; n_D^{20} 1.5006–1.5008. After a 3-g. interfraction there is obtained 41.4 g. (61% yield) of phenyl-nitromethane, b.p. 77–79°/1 mm.; n_D^{20} 1.5315. The phenylnitromethane is completely soluble in 20% aqueous sodium hydroxide.

[75] Kornblum and Ungnade, *Org. Syntheses*, **38**, 75 (1958).

Syntheses Employing Sodium Nitrite

Ethyl α-Nitrobutyrate. Detailed directions for the synthesis of this α-nitro ester in 68–75% yield from ethyl α-bromobutyrate are given in *Organic Syntheses*.[37]

1-Nitrooctane.[21] 1-Bromooctane (58 g., 0.30 mole) is poured into a stirred mixture of 600 ml. of dimethylformamide (DMF) and 36 g. of sodium nitrite (0.52 mole) immersed in a water bath maintained at room temperature, stirring is continued for 6 hours. The reaction mixture is then poured into 1.5 l. of ice water layered over with 100 ml. of petroleum ether (b.p. 35–37°). The aqueous phase is extracted four more times with 100-ml. portions of petroleum ether, after which the combined extracts are washed with water and dried over anhydrous magnesium sulfate. The petroleum ether is removed by distillation under reduced pressure, heat being supplied by a bath whose temperature is gradually raised to 65°. Rectification of the residue yields 13.6 g. (29%) of 1-octyl nitrite (b.p 37°/2 mm., n_D^{20} 1.4127), 2.8 g. of interfractions, and 28.2 g (60%) of 1-nitrooctane (b.p. 60°/1 mm., n_D^{20} 1.4324). When 1-iodooctane is used the reaction time is cut to 2½ hours.

2-Nitrooctane. *A*.[21] 2-Iodooctane (71.2 g., 0.30 mole) is poured into a stirred solution of 225 ml. of dimethyl sulfoxide (DMSO) and 36 g. of sodium nitrite (0.52 mole) contained in a 500-ml. flask immersed in a water bath held at room temperature. Stirring is continued for 4 hours. The reaction mixture is poured into 600 ml. of ice water layered over with 100 ml. of petroleum ether (b.p. 35–37°). The aqueous phase is separated and further extracted with four 100-ml. portions of petroleum ether. The combined extracts are washed with water and then dried over anhydrous magnesium sulfate. The petroleum ether solution is distilled through a small column, after which the residual liquid is rectified under reduced pressure. At 2 mm., 14.0 g. (30% yield) of 2-octyl nitrite (n_D^{20} 1.4089) distills at 32°, this is followed by a small fraction (3.9 g.) (b.p. 53–56°/1 mm.; n_D^{20} 1.4111–1.4382), after which 27 g. (58% yield) of 2-nitrooctane (b.p. 61°/1 mm.; n_D^{20} 1.4281) is obtained

B.[21] 2-Iodooctane (72 g., 0.30 mole) is poured into a stirred mixture of 600 ml. of DMF, 36 g. of sodium nitrite (0.52 mole), and 40 g. of urea (0.67 mole) in a 1-l. flask equipped with a sealed stirrer. The flask is stoppered, immersed in a water bath maintained at room temperature, and stirring is continued for 4 hours. The reaction mixture is then poured into 1.5 l. of ice water layered over with 100 ml. of petroleum ether (b.p. 35–37°). After separation of the upper layer, the aqueous phase is extracted repeatedly with petroleum ether. The combined extracts are then washed with two 75-ml. portions of 10% aqueous sodium thiosulfate, with 150 ml. of water, and are dried over anhydrous magnesium sulfate.

Using a small column, the petroleum ether is stripped off under reduced pressure, heat being supplied by a bath whose temperature is gradually raised to about 65°. The residual pale-blue liquid is transferred, with the aid of a little petroleum ether, to a 100-ml. flask. the column is attached, and the remaining solvent is removed under reduced pressure. Rectification of the residue yields 12.0–14.2 g. (25–30%) of 2-octyl nitrite (b.p. 30°/2 mm.; n_D^{20} 1.4091), 0.9–3.3 g. of interfractions. and 27.2–28.1 g. (57–60%) of 2-nitroöctane (b.p. 57°/1 mm.; n_D^{20} 1.4280).

Nitrocyclopentane.[22] Cyclopentyl bromide (22.0 g., 0.15 mole) is treated with a solution of 18 g. of sodium nitrite in 100 ml. of DMSO for 3 hours at 15°. On working up the reaction mixture in the same way as in the preceding example, 9.9 g. (58% yield) of nitrocyclopentane is isolated (b.p. 62°/8 mm.; n_D^{20} 1.4538).

Phenylnitromethane.[21] Benzyl bromide (51.3 g., 0.30 mole) is poured into a stirred mixture of 600 ml. of DMF, 36 g. of sodium nitrite (0.52 mole), and 40 g. of urea maintained at −20° to −15°. After 5 hours the reaction mixture is worked up as in the 1-nitroöctane preparation on p. 131 except that 700 ml. of diethyl ether is used for extraction. Rectification gives 13.1 g. (33% yield) of crude benzyl nitrite (b.p. 44°/5 mm.; n_D^{20} 1.5010–1.5024), 1.7 g. of interfractions. and 22.1 g. (55% yield) of phenylnitromethane (b.p. 76°/2 mm.; n_D^{20} 1.5316). The phenylnitromethane is completely soluble in 20% aqueous sodium hydroxide.

(+)-α-Phenylnitroethane.[35] In a 1-l. flask equipped with a stirrer, a drying tube containing potassium hydroxide, and a dropping funnel are placed 550 ml. of DMF (dried over calcium hydride), 35.6 g. (0.534 mole) of dry sodium nitrite, and 47.4 g. of dry urea. The reaction vessel is placed in an ice-salt bath, stirring is begun, and the solution is cooled to −18°. (+)-α-Phenylethyl bromide (65.1 g., 0.352 mole; $\alpha_D^{25} = +66.32$; neat, 1 dm.) is added dropwise over a 3- to 5-minute period. The flask is covered with a towel to exclude light. After 13 hours at −18° a negative test for organic halide* is obtained showing that the reaction is complete.† The reaction mixture is poured into 1 l. of ice water layered with 400 ml. of benzene. The aqueous layer is extracted with three 100-ml. portions of benzene and then with two 100-ml. portions of diethyl ether. The combined ether-benzene extracts are washed with four 75-ml. portions of water and dried over anhydrous magnesium

---

* This test is carried out by shaking several drops of the reaction solution with a mixture of about 1 ml. of water and 1 ml. of petroleum ether (b.p. 35–37°). The petroleum ether layer is isolated, most of the petroleum ether is removed by evaporation, and a drop of a saturated solution of silver nitrate in acetonitrile is added. A precipitate shows the presence of organic halide, whereas a cloudy, or clear, solution signifies the absence of organic halide.

† The reaction mixture is worked up in subdued light until the nitrite ester has been removed.

2-Nitrobutane.[42] With vigorous stirring, 65.2 ml. (2.4 moles) of 90% hydrogen peroxide is added dropwise fairly rapidly to 300 ml. of ice-cooled ethylene chloride. After addition of four drops of sulfuric acid catalyst, 292 g. (2.88 moles) of acetic anhydride is added to the cooled solution during 90 minutes. The mixture so obtained is stirred for 30 minutes at 0° and 30 minutes at room temperature. It is diluted with 200 ml. of ethylene chloride and heated rapidly to reflux. At this temperature a solution of 43.8 g. (0.6 mole) of *sec*-butylamine in 50 ml. of ethylene chloride is added dropwise over 1 hour. The reaction is very exothermic during this addition, and the system rapidly develops a blue color. After the amine has been added, the mixture is heated under reflux for 1 hour. It is then cooled, washed with two 500-ml. portions of cold 1:1 ammonia, and then with 500 ml. of water. The organic extract is dried over magnesium sulfate, and the major portion of solvent is removed by fractionation in a column packed with glass helices. The residue, still containing some solvent, is fractionated in a spinning band column; 40.2 g. (65%) of 2-nitrobutane (b.p. 64–66°/60 mm.; n_D^{20} 1.4043) is obtained.

The Oxidation of Oximes

Phenylnitromethane.[43] A solution of peroxytrifluoroacetic acid is prepared from 5.5 ml. (0.2 mole) of 90% hydrogen peroxide, 34.0 ml. (0.24 mole) of trifluoroacetic anhydride, and 50 ml. of acetonitrile. This is added over a 1¼-hour period to a well-stirred mixture of 2.0 g. of urea, 78 g. (0.55 mole) of dibasic sodium phosphate, and 12.1 g. (0.1 mole) of benzaldehyde oxime in 200 ml. of acetonitrile. The mixture is heated under gentle reflux during the addition and for 1 hour after the addition has been completed. It is then cooled and added to 400 ml. of water. The resulting solution is extracted with four 100-ml. portions of methylene chloride. The combined extracts are washed with three 100-ml. portions of 10% sodium bicarbonate solution and dried over magnesium sulfate. The solvent is evaporated under reduced pressure and the residual liquid is fractionated through a semimicro column.[76] After a small forerun has distilled, there is obtained 10.6 g. (77%) of colorless phenylnitromethane, b.p. 97–99°/4.0 mm.

4-Nitroheptane.[43] A solution of peroxytrifluoroacetic acid in acetonitrile prepared as described above is added over an 80-minute period to a well-stirred suspension of 47 g. (0.55 mole) of sodium bicarbonate in a solution of 2 g. of urea, 12.9 g. (0.1 mole) of di-*n*-propyl ketoxime, and 200 ml. of acetonitrile. Throughout the addition and for 1 hour after, the solution is heated under gentle reflux. It is then poured into 600 ml.

[76] Gould, Holzman, and Niemann, *Anal. Chem.*, **20**, 361 (1948).

of cold water and worked up as in the preceding preparation Fractionation of the product through a semimicro column[74] yields 9.3 g. (64%) of 4-nitroheptane, b p 58–69°/3 mm.

Nitrocyclobutane.[48] A solution of 16.1 g (0.19 mole) of cyclobutanone oxime and 40 g (0 47 mole) of sodium bicarbonate dissolved in 230 ml of water is added during 30 minutes to a stirred solution of 85 g. (0 47 mole) of N-bromosuccinimide *dissolved in 200 ml of water The reaction mixture is maintained at 0–10°* by an ice-salt bath and *is stirred 30 minutes after addition of the oxime solution. The product is collected* by five extractions with 50-ml portions of petroleum ether (b.p. 20–40°) The combined extract *is* concentrated on a steam bath, and the blue oil *is* oxidized by shaking at room temperature with a mixture of 150 ml. of concentrated nitric acid (sp gr 1.42) and 70 ml. of 30% hydrogen peroxide until the blue color *is completely removed. The reaction mixture is* diluted with water and the bromonitrocyclobutane is extracted with petroleum ether (b.p. 20–40°) *After washing with dilute sodium hydroxide solution and water, the solvent is removed by distillation. The crude bromonitro compound (about 23 g.) is added dropwise to a stirred refluxing mixture of 38 g. (1.0 mole) of sodium borohydride in* 300 ml. of methanol and 100 ml. of water (about 30 minutes are required). *The methanol is removed by steam distillation and the aqueous solution is* acidified by addition of 75 g. of hydroxylamine hydrochloride The nitro compound is collected by continuous extraction with petroleum ether (b.p. 20–40°) *After drying over anhydrous sodium sulfate, the extract yields 42 g (23%) of pure nitrocyclobutane (b p. 77–78°/40 mm.; n_D^{20} 1.4413)*

Nitrations Employing Nitrate Esters

Phenylnitromethane. Benzyl cyanide *is nitrated with methyl nitrate* and the resulting salt is hydrolyzed and decarboxylated; the over-all yield of phenylnitromethane is 50–55%. Detailed directions are given in *Organic Syntheses.*[45]

Dipotassium 2,5-Dinitrocyclopentanane.[48] A stirred solution of 18.45 g. (0.165 mole) of potassium t-butoxide (rendered free of t-butyl alcohol by sublimation at 220°/1 mm.) in 90 ml. of tetrahydrofuran (purified by refluxing over sodium hydroxide and then distilling from potassium metal under nitrogen) *is cooled to* −30° by means of a solid carbon dioxide bath, and 4.2 g. (0.05 mole) of cyclopentanone dissolved in 70 ml. of tetrahydrofuran *is added dropwise* over 30 minutes. A solution of 14.6 g. (0 11 mole) of amyl nitrate in 35 ml. of tetrahydrofuran is then added dropwise over 30 minutes with the temperature maintained

at $-30°$. The bath is removed and the reaction mixture is allowed to warm to $25°$, with stirring.

As soon as the reaction mixture reaches room temperature, it is filtered through a pressure filtration apparatus, nitrogen being used to supply the pressure. The residue, dipotassium 2,5-dinitrocyclopentanone, is washed successively with 70 ml. of tetrahydrofuran, 50 ml. of methanol, and 50 ml. of ether and is recrystallized from 30% aqueous potassium hydroxide. The green crystals are washed with methanol until the washings are colorless and neutral. The yield of analytically pure salt after drying at $56°/1$ mm. is 55%.

Nitrations Employing Nitric Acid

Diethyl Nitromalonate.[63] Diethyl malonate (80.0 g., 0.5 mole) is placed in a 500-ml. three-necked flask fitted with dropping funnel, stirrer, thermometer, and an outlet protected by a drying tube. The flask is cooled by tap water at $12°$, and 184 ml. of fuming nitric acid (d. 1.5) is added at a rate sufficient to maintain the temperature between $15°$ and $20°$. The addition requires 1 hour, after which time the mixture is stirred for $3\frac{1}{2}$ hours at $15°$. The solution is poured onto 1 l. of ice and water and the ester extracted with a 200- and a 100-ml. portion of toluene.

The combined toluene extracts are washed twice with water and then with 200-ml. portions of 5% aqueous urea until a starch-potassium iodide test for oxides of nitrogen in the wash is negative. The toluene solution is extracted with 10% aqueous sodium carbonate in portions until acidification of a test portion of extract shows that it contains no nitro ester. The sodium carbonate extracts are combined and washed once with 200 ml. of toluene. The aqueous solution is then carefully acidified to Congo red paper with concentrated hydrochloric acid, with cooling by the occasional addition of ice.

The ester is collected by extraction with 500-, 200-, and 100-ml. portions of toluene. The toluene solution is washed with two 200-ml. portions of water and then with 5% aqueous urea, again being checked with starch-potassium iodide test paper for the complete absence of oxides of nitrogen. The toluene solution is dried over magnesium sulfate. The yield of ester is determined by weighing the toluene solution, taking an aliquot, adding an equal volume of ethanol, and titrating the nitro ester with N sodium hydroxide to a phenolphthalein end point. The assay shows that the yield is 94.1 g. or 91.7%. If analytically pure ester is desired, it may be obtained by concentrating and distilling. The pure ester $(n_D^{21}$ 1.4274) boils at $81–83°/0.3$ mm.

TABULAR SURVEY

Each of the following tables, II through VII, is concerned with a general method of preparing nitro compounds. Within a given table the nitro compounds are divided into three groups: primary, secondary, and tertiary. Within each of these groups (except in Table VI) compounds are listed in the following sequence:

Straight-chain nitro compounds
Branched-chain nitro compounds
Alicyclic nitro compounds
Unsaturated nitro compounds
Benzylic and other arylated nitro compounds
Nitro ketones
Nitro acids
Nitro esters
Nitro nitriles
Miscellaneous nitro compounds
Dinitro compounds

In Table VI the sequence is:

Nitro compounds devoid of other functional groups
Nitro ketones
Nitro esters
Nitro nitriles
Miscellaneous nitro compounds

The literature through June, 1959, has been covered in this survey.

Throughout these tables a dash in the yield column corresponds to an unspecified yield and is different from 0% yield which, when established, is always explicitly stated.

TABLE II

Nitro Compounds Prepared with Silver Nitrite

Nitro Compound (Yield, %) RNO_2	Halide Employed RX	Yield of Nitrite Ester, % RONO	References
CH_3NO_2 (71)	I	16	77
$C_2H_5NO_2$ (—)	I	—	1
$n\text{-}C_3H_7NO_2$ (67)	Br	16	78
(70)	I	—	79
$n\text{-}C_4H_9NO_2$ (0)	Cl	—	78
(73)	Br	13	0
(74)	I	12	0
$n\text{-}C_5H_{11}NO_2$ (67)	Br	—	80
$n\text{-}C_6H_{13}NO_2$ (0)	Cl	—	0
(70, 69)	Br	10	0, 8
(78)	I	13	0
$n\text{-}C_7H_{15}NO_2$ (70, 61)	Br	11	0, 80
(82)	I	10	0
$n\text{-}C_8H_{17}NO_2$ (0)	Cl	—	0
(80)	Br	14	75
(84)	I	11	0
$n\text{-}C_{10}H_{17}NO_2$ (—)	I	—	81
$i\text{-}C(CH_3)_2NO_2$ (39)	Br	—	82
(70)	I	—	82
$i\text{-}C(CH_3)_2NO_2$ (58)	Br	—	82
(70)	I	—	82
$i\text{-}C(CH_3)_2NO_2$ (73)	Br	—	82
(70)	I	—	82
$i\text{-}C(CH_3)_2NO_2$ (54)	Br	—	82

Compound		Halide			Yield
$HOCH_2CH_2NO_2$ (62)	I				83
$CH_2ClCHClCH_2CH_2NO_2$ (64)	I		14		83
$(CH_3)_2CHCH_2NO_2$ (18)†		Br	20		6
$(CH_3)_2CHCH_2CH_2NO_2$ (59, 44)	I		19		6,80
$(CH_3)_2CHCH_2CH_2CH_2NO_2$ (72, 61)		Br	16		6,80
$(CH_3)_3CCH_2NO_2$ (78)	I				6,1
$(CH_3)_3CCH_2CH_2NO_2$ (63)	I				8,6
$CH_2=CHCH_2NO_2$ (65)‡	I	Br			7
$CH_2=C(CH_3)CH_2CH_2NO_2$ (80)	I	Br			84
$C_4H_7CH_2NO_2$ (—)	I	Cl			85
— (61)	I	Br	23		9
$p\text{-}H_3C_6H_4CH_2NO_2$ (38)	I	Br			86
$p\text{-}O_2NC_6H_4CH_2NO_2$ (75)	I	Br			87
—	I	Br		5	8
$p\text{-}CH_3OC_6H_4CH_2NO_2$ (28)	I	Br			88
$p\text{-}CH_3C_6H_4CH_2CH_2NO_2$ (45)	I			55	8
$C_6H_5CH(CH_3)NO_2$ (56)	I			57	8
$C_6H_5CH_2CH_2NO_2$ (50)	I				89
$C_6H_5CHClNO_2$ (55)	I				89
$C_6H_5CH(CH_3)NO_2$ (70)	I				89
$C_6H_5C(CH_3)_2NO_2$ (50)	I				89
$CH_3COCH_2NO_2$ (—)	I				89
$C_6H_5COCH_2NO_2$ (—)	I		2		90
$O_2NCH(CH_3)CO_2H$ (—)	I				91
					92

Note: References 77 to 108 are on p. 166.

* After 5 days, 63% of the halide was recovered.
† After 3 days, 90% of the halide was recovered.
‡ This reaction was run in diethyl ether at 0° for 12 hours; b.p. of nitro compound, 39–40°/20 mm.; n_D^{20} 1.4260.

TABLE II—*Continued*

Nitro Compounds Prepared with Silver Nitrite
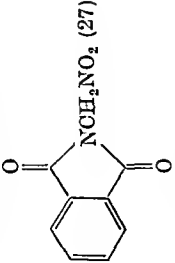
Nitro Compound (Yield, %) RNO₂	Halide Employed RX	Yield of Nitrite Ester, % RONO	References
$O_2NCH_2CO_2C_2H_5$ (77)	I	—	14
$O_2NCH_2CH_2CO_2C_2H_5$ (—)	I	—	92
[phthalimide] NCH_2NO_2 (27)	Br	—	93
$O_2NCH_2CH_2CH_2NO_2$§ (—)	$I(CH_2)_2I$	—	94
$O_2N(CH_2)_3NO_2$ (37)	$I(CH_2)_3I$	—	9, 95
$O_2N(CH_2)_4NO_2$ (41–46)	$I(CH_2)_4I$	—	9
$O_2N(CH_2)_5NO_2$ (45)	$I(CH_2)_5I$	—	9
$O_2N(CH_2)_6NO_2$ (46–48)	$I(CH_2)_6I$	—	9
$O_2N(CH_2)_7NO_2$ (60)	$I(CH_2)_7I$	—	96
$O_2N(CH_2)_{10}NO_2$ (50)	$I(CH_2)_{10}I$	—	97
$(CH_3)_2CHNO_2$ (0)	Cl	—	10
(19–26)	Br	24–34‖	10
(15–23)	I	25–35‖	10, 98
$CH_3CH_2CH(CH_3)NO_2$ (0)	Cl	—	10
(19–24)	Br	27–37¶	10
(10–15)	I	30–35¶	10
$(CH_3CH_2CH_2)_2CHNO_2$ (7–15)	Br	22–29¶	10
(9)	I	27¶	10
$CH_3(CH_2)_5CH(CH_3)NO_2$ (0)	Cl	—	10
(17–23)	Br	18–25‖	10

TABLE III

Nitro Compounds Prepared with Sodium Nitrite

Nitro Compound (Yield, %) RNO₂	Halide Employed RX	Solvent	References
$CH_3(CH_2)_3NO_2$ (46)	Methanesulfonate	DMF	21
$CH_3(CH_2)_6NO_2$ (00)	Br	DMF	21
(01)	I	DMF	21
$CH_3(CH_2)_7NO_2$ (00)	Br	DMF	21
(06)		DMSO	22
(00)		DMF	21
(00)		DMF	21
(45)	Tosylate	DMF	21
$CH_3(CH_2)_9NO_2$ (57)	I	DMF	21
$C_6H_5CH_2NO_2$ (55)	Br	DMF	15
$p\text{-}O_2NC_6H_4CH_2NO_2$ (22)	Br	DMF	21
$C_6H_5(CH_2)_3NO_2$ (58)	I	DMF	81
$CH_3COCH_2CH_2NO_2$ (47)	Cl	DMF	81
$CH_3CH_2COCH_2CH_2NO_2$ (48)	Cl	DMF	81
$C_6H_5COCH_2CH_2NO_2$ (87)	Br	DMF	15
$O_2NCH_2CO_2C_2H_5$ (0)	Br	DMF	21
$CH_3(CH_2)_5CH(CH_3)NO_2$ (58)	Br	DMF	22
(46)		DMSO	21
(00)	I	DMF	22
(58)		DMSO	21
$(CH_3CH_2CH_2)_2CHNO_2$ (61)	Br	DMF	21
(02)	I	DMF	101
$CH_3(CH_2)_{10}CH(CH_3)NO_2^*$ (—)	I	DMF	21
Nitrocyclopentane (57)	Br	DMF	22
(58)		DMSO	21
(55)	I	DMF	

Nitrocyclohexane (0)	Br	DMF	21
(0)	I	DMF	21
Nitrocycloheptane (55)	Br	DMF	21
(55)	I	DMF	21
$C_6H_5CH(CH_3)NO_2$ (45)	Br	DMF	35
$CH_3CH(NO_2)CO_2C_2H_5$ (08)	Cl	DMSO	28
$CH_3CH(NO_2)CO_2C_2H_5$ (60)	Br	DMSO	28
		DMF	28
$CH_3CH(NO_2)CO_2C_2H_5$ (52)	I	DMF	28
$CH_3CH_2CH(NO_2)CO_2C_2H_5$ (08–75)	Br	DMF	27, 28
(83)		DMSO	28
$CH_3(CH_2)_3CH(NO_2)CO_2C_2H_5$ (87)	Br	DMSO	28
$CH_3(CH_2)_3CH(NO_2)CO_2C_2H_5$ (70)	Br	DMSO	28
$(CH_3)_2CHCH(NO_2)CO_2C_2H_5$ (74)	Br	DMF	28
(75)		DMSO	28
$C_6H_5CH(NO_2)CO_2C_2H_5$ (70)	Br	DMF	28
$(CH_3)_2CSO_2$ ‡ (0)	Cl	DMF	28
	Br	DMF	21
$(CF_3)_2CSO_2CO_2C_2H_5$ (91)	Br	DMSO	28
$(CH_3)_2CSO_2)CN$ (52)	Br	DMF	28
		DMF	19

Note. Reference 77 to 104 are on p. 156.
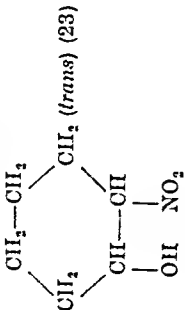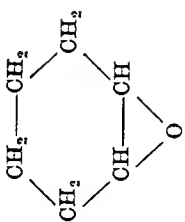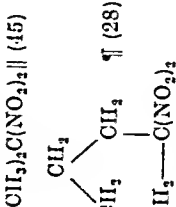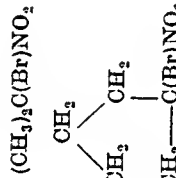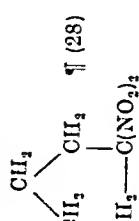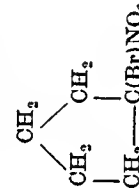
* This reaction was conducted at −18°. † 2-Nitroindecane had b.p. 122° 1 mm., n_D^{20} 1.4421. In DMSO, at 11°, a 22% yield of α-phenylnitroethane was obtained.

‡ Isobutylene was obtained in 60% yield.

§ Isobutylene was obtained in 73% yield.

TABLE III—*Continued*

Nitro Compounds Prepared with Sodium Nitrite

Nitro Compound (Yield, %) RNO$_2$	Halide Employed RX	Solvent	References
(trans cyclohexane ring bearing OH and NO$_2$) (23)	(cyclohexene oxide ring, O)	DMSO	33
$(CH_3)_2C(NO_2)_2$ ‖ (45)	$(CH_3)_2C(Br)NO_2$	DMF	34
(cyclobutane ring, C(NO$_2$)$_2$) ¶ (28)	(cyclobutane ring, C(Br)NO$_2$)	DMF	34
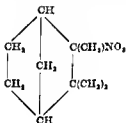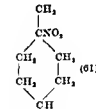
Note: References 77 to 108 are on p. 156.

‖ Urea was added and the reaction was conducted at 70–80° for 1 day.

¶ Urea was added and the reaction was conducted at 40° for 4 days.

TABLE IV

NITRO COMPOUNDS PREPARED BY THE OXIDATION OF AMINES

$$RNH_2^* \rightarrow RNO_2$$

Nitro Compound (Yield, %)	Oxidizing Agent	Reference
$CH_3(CH_2)_5NO_2$ (33)	CH_3CO_2OH	42
$CH_3CH_2CH(CH_2)_2NO_2$ (65)	CH_3CO_2OH	42
Nitrocyclohexane (70)	CH_3CO_2OH	42
$(CH_3)_2CNO_2$ (83)	$KMnO_4$	39
$(CH_3)_2CHC(CH_3)_2NO_2$ (71)	$KMnO_4$	39
$(CH_3)_2CHCH_2C(CH_3)_2NO_2$ (82)	$KMnO_4$	39
$(CH_3)_3CCH_2C(CH_3)_2NO_2$ (77)	$KMnO_4$	39
(87)	CH_3CO_2OH	42
1-Nitro-1-methylcyclopentane (72)	$KMnO_4$	39
1-Nitro-1-methylcyclohexane (73)	$KMnO_4$	39
1-Nitro-1,4-dimethylcyclohexane (70)	$KMnO_4$	39

(—)	$KMnO_4$	13

(61)	$KMnO_4$	39

$(CH_3)_3CNO_2$		
$(C_2H_5)_3CNO_2$ (0)	$KMnO_4$	39

Note: References 77 to 108 are on p. 156.

* The amine used corresponded in structure to the nitro compound formed.
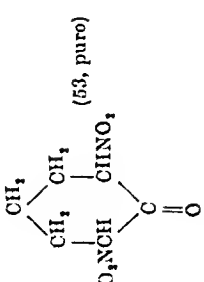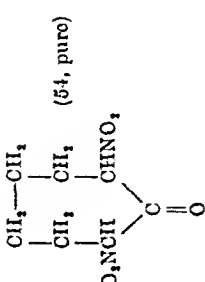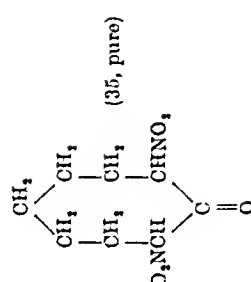
TABLE V

NITRO COMPOUNDS PREPARED BY THE OXIDATION OF OXIMES
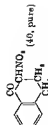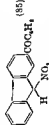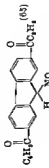
$$RCH{=}NOH \rightarrow RCH_2NO_2$$
$$R_2C{=}NOH \rightarrow R_2CHNO_2$$

Nitro Compound (Yield, %)	Oxime Oxidized	Reagents, Remarks	Reference
1-Nitrobutane (0)	Butanal	NaOBr	45
1-Nitroheptane (72)	Heptanal	$CF_3CO_3H + NaHCO_3$	43
1-Nitroöctane (63)	Octanal	$CF_3CO_3H + NaHCO_3$	43
Phenylnitromethane (77)	Benzaldehyde	$CF_3CO_3H + Na_2HPO_4$	43
ω-Nitroacetophenone (76)	Phenylglyoxal aldoxime	CF_3CO_3H	43
Ethyl nitroacetate (40)	Ethyl α-oximinoacetoacetate	CF_3CO_3H	43
2-Nitropropane (0)	Acetone	NaOBr and then aqueous ethanolic KOH	45
2-Nitrobutane (47)	Butanone	$CF_3CO_3H + NaHCO_3$	43
2-Nitropentane (43)	Methyl n-propyl ketone	$CF_3CO_3H + NaHCO_3$	43
(38)		N-Bromosuccinimide and then $NaBH_4$	46
3-Nitropentane (29)	Diethyl ketone	N-Bromosuccinimide and then $NaBH_4$	46
2-Nitrohexane (19)	Methyl n-butyl ketone	N-Bromoacetamide and then $NaBH_4$	46
3-Nitrohexane (25)	Ethyl n-propyl ketone	N-Bromoacetamide and then $NaBH_4$	46
2-Nitroheptane (59)	2-Heptanone	$CF_3CO_3H + NaHCO_3$	43
(16)		N-Bromoacetamide and then $NaBH_4$	46
3-Nitroheptane (29)	3-Heptanone	N-Bromoacetamide and then $NaBH_4$	46
4-Nitroheptane (64)	4-Heptanone	$CF_3CO_3H + NaHCO_3$	43
(28)		N-Bromoacetamide and then $NaBH_4$	46
2-Nitroöctane (10)	2-Octanone	N-Bromoacetamide and then $NaBH_4$	46
2-Nitro-3-methylbutane (49)	Methyl isopropyl ketone	N-Bromoacetamide and then $NaBH_4$	46
(48)		$CF_3CO_3H + NaHCO_3$	43
3-Nitro-2,2-dimethylbutane (30)	Pinacolone	N-Bromosuccinimide and then $NaBH_4$	46
Nitrocyclobutane (23)	Cyclobutanone	N-Bromosuccinimide and then $NaBH_4$	44

Nitrocyclopentane (90)	Cyclopentanone	CF₃CO₂H + Na₂HPO₄	43
Nitrocyclobutane (55)		N-Bromosuccinimide and then NaBH₄	44
(50)	Cyclohexanone	CF₃CO₂H + Na₂HPO₄	43
2-Nitro-1-methylcyclohexane (30)	2-Methylcyclohexanone	N-Bromosuccinimide and then NaBH₄	44
4-Nitro-1-methylcyclohexane (22)	4-Methylcyclohexanone	N-Bromosuccinimide and then NaBH₄	44
Nitrocycloheptane (51)	Cycloheptanone	N-Bromosuccinimide and then NaBH₄	44
(30)		CF₃CO₂H + Na₂HPO₄	43
		N-Bromosuccinimide and then NaBH₄	44

(80)

	Camphor	KOH + Br₂ followed by aqueous alcoholic KOH	102
		KOH	

α-Nitroindanone (0)	α-Indanone	NaOH + Br₂	45
(C₂H₅)₂C(NO₂) (0)	Benzophenone	NaOH + Br₂	45
9-Nitrofluorene (0)	Fluorenone	NaOH + Br₂	45
α-Phenylnitroethane (90)	Acetophenone	CF₃CO₂H + Na₂HPO₄	43
Diethylnitromethane (90)	Diethyl mesoxalate	CF₃CO₂H	43
Nitromalonamide (10)	Mesoxalamide	CF₃CO₂H	43

Note References 77 to 108 are on p. 155.

TABLE VI—*Continued*
Nitrations Employing Nitrate Esters

Salt of Nitro Compound (Yield, %)	Compound Nitrated	Base	Nitrate Ester	Reference
(53, pure)	Cyclohexanone	KOC(CH₃)₃	Amyl	55
(54, pure)	Cycloheptanone	KOC(CH₃)₃	Amyl	55
(35, pure)	Cycloöctanone	KOC(CH₃)₃	Amyl	55

Compound	Structure	Reagent	Solvent	Ref.
α-Tetralone	(structure) CHNO$_2$ ... CH$_2$CH$_2$ (40, pure)	KOC(CH$_3$)$_3$	Amyl	55
2 Benzoylfluorene	(structure) COC$_6$H$_5$ (85)	KOC$_2$H$_5$	Ethyl	108
2,7 Dibenzoylfluorene	(structure) C$_6$H$_5$CO ... H NO$_2$ ... NO$_2$ ... COC$_6$H$_5$ (85)	KOC$_2$H$_5$	Ethyl	109
p CH$_3$C$_6$H$_4$SCH$_2$COC$_6$H$_5$	Diethyl malonate O$_2$NCH(CO$_2$C$_2$H$_5$)$_2$ (42,* pure)	NaOC$_2$H$_5$ NaH	Ethyl Acetone	55 62
CH$_3$COCH(CO$_2$C$_2$H$_5$)$_2$	O$_2$NCH(CO$_2$C$_2$H$_5$)$_2$ (52,* pure)	NaH	Acetone cyanohydrin	62
CH$_2$CO$_2$C(CH$_3$)$_3$	O$_2$NCH$_2$CO$_2$CMe$_3$ (0)	NaH	Acetone cyanohydrin	62
(CH$_3$CO)$_2$CH$_2$	O$_2$NCH(CO$_2$C$_2$H$_5$)$_2$ (0)	NaH	Acetone cyanohydrin	62
CH$_3$CH(CO$_2$C$_2$H$_5$)$_2$	CH$_3$CH(NO$_2$)CO$_2$C$_2$H$_5$ (56,* pure)	NaH	Acetone cyanohydrin	62
CH$_3$CH$_2$CH(NO$_2$)CO$_2$C$_2$H$_5$	(51,* pure)	NaH	Acetone cyanohydrin	62
CH$_3$CH$_2$CH$_2$CH(NO$_2$)CO$_2$C$_2$H$_5$	(46,* pure)	NaH	Acetone cyanohydrin	62
CH$_3$COCH(CH$_2$CH$_2$CO$_2$C$_2$H$_5$)		NaH	Acetone cyanohydrin	62

Note , not the salt.

* Thus is the yield of the nitro compound, not the salt.

TABLE VI—Continued

Nitrations Employing Nitrate Esters

Salt of Nitro Compound (Yield, %)	Compound Nitrated	Base	Nitrate Ester	Reference
n-$C_4H_9CH(NO_2)CO_2C_2H_5$ (54,* pure)	n-$C_4H_9CH(CO_2C_2H_5)_2$	NaH	Acetone cyanohydrin	62
n-$C_4H_9CH(NO_2)CO_2C_2H_5$ (50,* pure)	$CH_3COCH(n$-$C_4H_9)CO_2C_2H_5$	NaH	Acetone cyanohydrin	62
n-$C_5H_{11}CH(NO_2)CO_2C_2H_5$ (46,* pure)	n-$C_5H_{11}CH(CO_2C_2H_5)_2$	NaH	Acetone cyanohydrin	62
n-$C_5H_{11}CH(NO_2)CO_2C_2H_5$ (70,* pure)	$CH_3COCH(n$-$C_5H_{11})CO_2C_2H_5$	NaH	Acetone cyanohydrin	62
i-$C_4H_9CH(NO_2)CO_2C_2H_5$ (47,* pure)	i-$C_4H_9CH(CO_2C_2H_5)_2$	NaH	Acetone cyanohydrin	62
i-$C_5H_{11}CH(NO_2)CO_2C_2H_5$ (60,* pure)	i-$C_5H_{11}CH(CO_2C_2H_5)_2$	NaH	Acetone cyanohydrin	62
$ClCH_2CH_2CH_2CH(NO_2)CO_2C_2H_5$ (40,* pure)	$ClCH_2COCH(CH_2CH_2CH_2Cl)CO_2C_2H_5$	NaH	Acetone cyanohydrin	62
$CH_2{=}CHCH_2CH(NO_2)CO_2C_2H_5$ (45,* pure)	$CH_2{=}CHCH_2CH(CO_2C_2H_5)_2$	NaH	Acetone cyanohydrin	62
$CH_2{=}CHCH_2CH(NO_2)CO_2C_2H_5$ (53,* pure)	$CH_3COCH(CH_2CH{=}CH_2)CO_2C_2H_5$	NaH	Acetone cyanohydrin	62
$C_6H_5CH_2CH(NO_2)CO_2C_2H_5$ (67,* pure)	$C_6H_5CH_2CH(CO_2C_2H_5)_2$	NaH	Acetone cyanohydrin	62
$O_2NCH(CO_2C_2H_5)_2$ (54,* pure)	Diethyl malonate	NaH	Acetone cyanohydrin	62
O_2NCH_2CN (0)	CH_3CN	$KOC(CH_3)_3$	Amyl	56
$CH_3CH_2CH(NO_2)CN$ (44, pure)	$CH_3CH_2CH_2CN$	$KOC(CH_3)_3$	Amyl	56
$CH_3(CH_2)_3CH(NO_2)CN$ (55, pure)	$CH_3(CH_2)_4CN$	$KOC(CH_3)_3$	Amyl	56
$O_2NCH(CN)CH_2CH_2CH_2CH(CN)NO_2$ (93, pure)	$NC(CH_2)_4CN$	$KOC(CH_3)_3$	Amyl	56
$O_2NCH(CN)CH_2CH_2CH_2CH_2CH(CN)NO_2$ (46, pure)	$NC(CH_2)_5CN$	$KOC(CH_3)_3$	Amyl	56
$O_2NCH(CN)CH_2CH_2CH_2CH_2CH_2CH(CN)NO_2$ (67, pure)	$NC(CH_2)_6CN$	$KOC(CH_3)_3$	Amyl	56

	XC(Q)CH₄CS	KOC(Cl₄)₃	Am,l	
O₂NCH(CN)CH₂CH₂CH₂CH₂CH₂CH(CN)NO₂ (48, pure)	Benzyl cyanide			58
C₆H₅CH(CN)NO₂ (75–82)	o·CH₃C₆H₄CH₂CN	NaOC₂H₅	Merh,l	49
o·CH₃C₆H₄CH(CN)NO₂ ("very good")	o·CH₃C₆H₄CH₂CN	NaOC₂H₅	Eh,l	104
m·CH₃C₆H₄CH(CN)NO₂ (ca. 75)	m·CH₃C₆H₄CH₂CN	NaOC₂H₅	Eh,l	104
p·CH₃C₆H₄CH(CN)NO₂ (—)	p·CH₃C₆H₄CH₂CN	NaOC₂H₅	Eh,l	104
o·CH₃C₆H₄CH(CN)NO₂ (ca. 70, crude)	o·BrC₆H₄CH₂CN	KOC₂H₅	Eh,l	50
p·BrC₆H₄CH(CN)NO₂ (over 90, crude)	p·BrC₆H₄CH₂CN	KOC₂H₅	Eh,l	50
α·C₁₀H₇CH(CN)NO₂ (—)	α·C₁₀H₇CH₂CN	NaOC₂H₅	Eh,l	104
β·C₁₀H₇CH(CN)NO₂ (—)	β·C₁₀H₇CH₂CN	NaOC₂H₅	Eh,l	104

(96)

p·CH₃C₆H₄SCH₂CO₂C₂H₅	p·CH₃C₆H₄SCH₂COC₂H₅	NaOC₂H₅	Eh,l	85

		KOH	Sel	59

Note References 77 to 108 are on p. 156.

* This is the yield of the nitro compound, not its salt.

TABLE VII

Nitro Compounds Prepared with Nitric Acid

Nitro Compound (Yield, %)	Compound Nitrated	Reference
$(C_6H_5)_2CHNO_2$* (ca. 50)	$(C_6H_5)_2CH_2$	70
$O_2NCH(CO_2C_2H_5)_2$ (ca. 92)	Diethyl malonate	63

        CHNO₂ (67)   1,3-Indanedione   66

$HC(NO_2)_2CO_2C_2H_5$ (11) $H_2C(CO_2H)CO_2C_2H_5$ 68

(84)   2-Phenyl-1,3-indanedione   67

(52–60)   2-(α-Naphthyl)-1,3-indanedione   67

(74)   67

* In this reaction nitrogen dioxide and oxygen were used in carbon tetrachloride at 70–75° with anhydrous cupric sulfate instead of nitric acid.

TABLE VII—Continued

NITRO COMPOUNDS PREPARED WITH NITRIC ACID

Nitro Compound (Yield, %)	Compound Nitrated	Reference
		67
$(C_4H_3)_2C(CN)NO_2$† (57)	$(C_6H_5)_2CHCN$	69
$CH_3C(NO_2)_2CO_2C_2H_5$ (17)	$CH_3CH(CO_2H)CO_2C_2H_5$	68
$C_2H_5C(NO_2)_2CO_2C_2H_5$ (17)	$C_2H_5CH(CO_2H)CO_2C_2H_5$	68
$n\text{-}C_4H_7C(NO_2)_2CO_2C_2H_5$ (8)	$n\text{-}C_4H_9CH(CO_2H)CO_2C_6H_5$	68
$(C_6H_5)_2C(NO_2)_2$‡ (ca. 30)	$(C_6H_5)_2CH_2$	70

Note References 77 to 108 are on p. 156.

† Dry nitrogen dioxide in chloroform at 15–20° was used instead of nitric acid.

‡ Nitrogen dioxide and nitric oxide were used in carbon tetrachloride with calcium nitrate instead of nitric acid.

REFERENCES FOR TABLES II–VII

[77] Sowden, *J. Biol. Chem.*, **180**, 55 (1949).

[78] Reynolds and Adkins, *J. Am. Chem. Soc.*, **51**, 279 (1929).

[79] Pauwels, *Rec. trav. chim.*, **17**, 27 (1898).

[80] Plummer and Drake, *J. Am. Chem. Soc.*, **76**, 2720 (1054).

[81] Frewing, *Proc. Roy. Soc.*, *(London)*, **A182**, 283 (1944).

[82] Pattison, Cott, Howell, and White, *J. Am. Chem. Soc.*, **78**, 3484 (1956).

[83] Noland and Hartman, *J. Am. Chem. Soc.*, **76**, 3227 (1954).

[84] Shechter and Shepherd, *J. Am. Chem. Soc.*, **76**, 3621 (1954).

[85] Holleman, *Rec. trav. chim.*, **13**, 405 (1804).

[86] Hantzsch and Schultze, *Ber.*, **29**, 700 (1896).

[87] Willard J. Jones, Ph.D. Thesis, Purdue University, 1959.

[88] Hantzsch and Veit, *Ber.*, **32**, 621 (1899).

[89] von Braun and Kruber, *Ber.*, **45**, 394 (1912).

[90] Lucas, *Ber.*, **32**, 3179 (1899).

[91] Lucas, *Ber.*, **32**, 601 (1899).

[92] Lewkowitsch, *J. prakt. Chem.*, [2] **20**, 159 (1879).

[93] Kissinger and Ungnade, *J. Org. Chem.*, **23**, 815 (1958).

[94] Ipatov, *J. Russ. Phys. Chem. Soc.*, **49**, 297 (1917) [*C.A.*, **17**, 3158 (1923)].

[95] Kispersky, Hass, and Holcomb, *J. Am. Chem. Soc.*, **71**, 516 (1949).

[96] von Braun and Danziger, *Ber.*, **46**, 103 (1913).

[97] von Braun and Sobecki, *Ber.*, **44**, 2531 (1911).

[98] Kohler, *J. Am. Chem. Soc.*, **38**, 898 (1016).

[99] Rosanow, *J. Russ. Phys. Chem. Soc.*, **47**, 501 (1915); **48**, 309 (1916) [*Chem. Zentr.*, **87**, I, 925 (1916); **95**, I, 2425 (1924)].

[100] Sonneborn and Wiselogle, *J. Am. Chem. Soc.*, **64**, 860 (1942).

[101] N. Kornblum and H. Larson, Unpublished work.

[102] Forster, *J. Chem. Soc.*, **77**, 254 (1900).

[103] Thiele, *Ber.*, **33**, 666 (1900).

[104] Wislicenus and Wren, *Ber.*, **38**, 502 (1905).

[105] Cooke and Macbeth, *J. Chem. Soc.*, **1938**, 1024.

[106] Thurston and Shriner, *J. Am. Chem. Soc.*, **57**, 2163 (1935).

[107] Shriner and Parker, *J. Am. Chem. Soc.*, **55**, 766 (1933).

[108] Ray and Palinchak, *J. Am. Chem. Soc.*, **62**, 2109 (1940).

CHAPTER 4

SYNTHESIS OF PEPTIDES WITH MIXED ANHYDRIDES

Noel F. Albertson

Sterling Winthrop Research Institute

CONTENTS

INTRODUCTION

A mixed acid anhydride, or mixed anhydride, is a dehydration product of two polyoxy acids. For a mixed anhydride to be of interest for

$$R_1CO_2H + R_2CO_2H \rightarrow R_1COOCOR_2 + H_2O$$
$$R_1CO_2H + R_2SO_2H \rightarrow R_1COOSO_2R_2 + H_2O$$
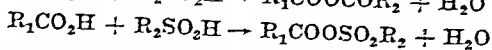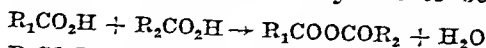
peptide synthesis one of the component acids must, in general, be an

$$R_1CONHCHR_2CO_2H + HA \rightarrow R_1CONHCHR_2COA + H_2O$$

$$R_1CONHCHR_2COA + H_2NCHR_2CO- \rightarrow$$

$$R_1CONHCHR_2CONHCHR_2CO- + HA$$
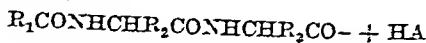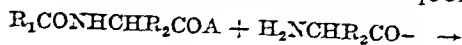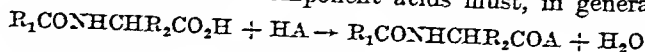
α-acylamino acid. The nature of the second component acid, HA, may vary widely.

In this chapter the term mixed anhydride will be used in a more general sense than ordinarily in order to emphasize the similarity of a number of procedures that have been found useful for the synthesis of peptides. Thus, in addition to conventional mixed anhydrides, derivable from polyoxy acids, reference will be made to "mixed anhydrides" otherwise recognizable as acyl halides, ethers, esters, thiol esters, O-acyl-isoureas and isoimides, etc.

In practice an α-acylamino acid mixed anhydride is usually prepared by reaction of an α-acylamino acid with an unsymmetrical anhydride that not only provides the second acid component but is also instrumental in causing the reaction to proceed in the desired direction.

$$R_1CONHCHR_2CO_2H + ClCOCH_3 \rightarrow R_1CONHCHR_2COOCOCH_3 + HCl$$
$$R_1CONHCHR_2CO_2H + ClCOOC_2H_5 \rightarrow R_1CONHCHR_2COOCOOC_2H_5 + HCl$$
$$R_1CONHCHR_2CO_2H + ClP(OC_2H_5)_2 \rightarrow$$

$$R_1CONHCHR_2COOP(OC_2H_5)_2 + HCl$$
$$3R_1CONHCHR_2CO_2H + P(SC_6H_4NO_2\text{-}p)_2 \rightarrow$$

$$3R_1CONHCHR_2COSC_6H_4NO_2\text{-}p + H_3PO_3$$
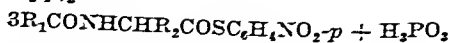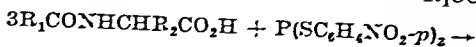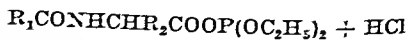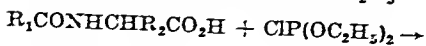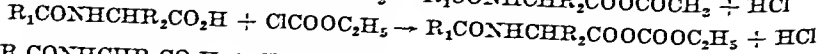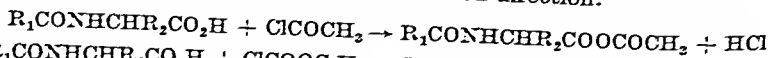
This chapter is limited to a review of the chemistry of the acyclic α-acylamino acid mixed anhydrides, excluding the well-known α-acyl-amino acid chlorides and azides which have already been the subject of

an excellent review.[1] In general, discussion of the application of α-acylamino acid mixed anhydrides will be limited to non-polymeric peptide bond formation and will not be concerned with acylations other than those leading to the formation of a peptide bond.

GENERAL CONSIDERATIONS

Nature of the Reaction

Formation of the α-Acylamino Acid Mixed Anhydride. In general, in the displacement reaction between the α-acylamino acid anion and an unsymmetrical anhydride the less reactive α-acylamino anhydride is formed with the elimination of the stable anion corresponding to the stronger acid.[2]

Amide Bond Formation. In the reaction of the α-acylamino anhydride with an amine, the amine behaves as the nucleophile and the acylating species as the electrophilic reagent. In an anhydride of the type $R_1CONHCHR·COOCOR_2$, the amine may attack at either anhydride carbonyl. If $R_2CONHCHR_1$— is the more strongly electron-attracting group, the adjacent carbonyl will be more positively charged than that adjacent to R_1 and the desired amide bond formation will predominate.[3,4] The base strength of the attacking amine may also be important in determining the major products of the reaction.[5]

The effect of the solvent upon the course of peptide synthesis has received little attention. However, in analogous reactions involving simpler unsymmetrical anhydrides, solvents are known to have considerable effect. The mixed anhydride of acetic and propionic acid reacts with aniline in an anhydrous medium to give a 90% yield of propionanilide, whereas in an aqueous medium propionylation decreases and the yield of acetanilide rises to 32%.[6] Similar results were obtained in the reaction of aniline with the mixed anhydride of acetic and chloroacetic acid; the ratio of chloroacetylation to acetylation decreased considerably with variation of the solvent in the order benzene, acetone, and aqueous acetone.[3,4]

The yield of acylations carried out in water is influenced by the pH of the solution. In non-aqueous solvents the rate may be influenced by the addition of acids or bases. These factors will be considered more fully under the individual α-acylamino mixed anhydrides

[1] Fruton, *Advances in Protein Chem.* **5**, 1 (1949).
[2] Cf Corby, Kenner, and Todd, *J Chem. Soc.*, 1952, 1234
[3] Emery and Gold, *J Chem. Soc.*, 1950, 1443, 1447
[4] Emery and Gold, *J Chem. Soc.*, 1950, 1455.
[5] Kenner, in *Symposium on Peptide Chemistry*, Special Publ. No. 2, The Chem Soc (London), 1955.
[6] Ellok and Gault, *Compt. rend.*, **238**, 2428 (1954)

Structural Factors

Structure of the Anhydride. The effect of varying the alkyl group R_2 in mixed α-acylamino anhydrides of the general formula $C_6H_5CH_2OCONHCHR_1COOCOR_2$ has been determined by reaction of 25 mixed anhydrides, derived from carbobenzyloxyglycine and various aliphatic acids, with aniline. The effectiveness of the mixed anhydride $C_6H_5CH_2OCONHCH_2COOCOR_2$ in producing carbobenzyloxyglycyl-anilide decreases with decreasing steric requirement of the group R_2. These results agree with those predicted by Newman's rule of six.[7] Thus Vaughan and Osato[8] found that those anhydrides, in which R_2 is derived from diethylacetic acid and isovaleric acid, having the highest six number, gave the highest yield of carbobenzyloxyglycylanilide (85% and 83% respectively). The isocaproic and lauric acid mixed anhydrides with six numbers only half as great as isovaleric acid gave yields of the above anilide of only 36% and 31%, respectively. However, the anhydride from trimethylacetic acid (six number of zero) and carbobenzyloxyglycine gave a 72% yield of carbobenzyloxyglycylanilide. In this instance, it is possible that the positive inductive effects of the alkyl groups play the major role in determining the course of the reaction.

No corresponding systematic study of the effect of changing the steric environment around the amino acid carbonyl by varying the amino acid side chain has yet been made.

In most cases the α-amino protecting group is carbobenzyloxy or carbobenzyloxyaminoacyl, although many others have been used. When the protecting group is trityl, steric hindrance generally prevents formation of an anhydride: trityl amino acids other than glycine or alanine apparently fail to form mixed anhydrides with ethyl chloroformate,[9, 10] although they will form mixed anhydrides with dicyclohexylcarbodiimide.[11, 12]

Formylglycyl ethyl carbonate reacts with ethyl p-aminobenzoate to form primarily the urethan I, whereas acetylglycyl ethyl carbonate forms the expected amide II.[13] However, other formylamino acid alkyl

$$HCONHCH_2COOCOOC_2H_5 + p\text{-}H_2NC_6H_4CO_2C_2H_5 \rightarrow$$

$$p\text{-}C_2H_5O_2CHNC_6H_4CO_2C_2H_5$$

$$1 \ (55\%)$$
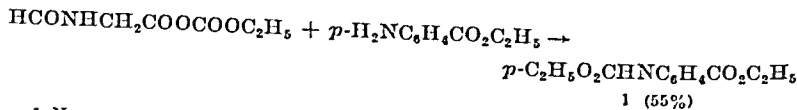
[7] Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950).

[8] Vaughan and Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951).

[9] Hillmann-Elies, Hillmann, and Jatzkewitz, *Z. Naturforsch.*, **8B**, 445 (1953).

[10] Amiard, Heymès, and Velluz, *Bull. soc. chim. France*, **1955**, 191.

[11] Amiard, Heymès, and Velluz, *Bull. soc. chim. France*, **1955**, 1464.

[12] Amiard and Goffinet, *Bull. soc. chim. France*, **1957**, 1133.

[13] King, Clark-Lewis, Kidd, and Smith, *J. Chem. Soc.*, **1954**, 1039.

$$CH_3CONHCH_2COOCOOC_2H_5 + p-H_2NC_6H_4CO_2C_2H_5 \rightarrow$$
$$CH_3CONHCH_2CONHC_6H_4CO_2C_2H_5$$
$$\text{II (52\%)}$$

carbonates react in the normal manner although yields are frequently low.

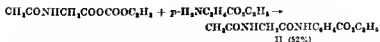Low yields (30–40%) of product have been obtained in the coupling of sodium glycinate with the mixed anhydrides $ClCH_2CONHCH$-$[CH_2CH_2CH(SC_2H_5)_2]COOCOOC_2H_5$, and $ClCH_2CONHCH_2COOCOOC_2H_5$, derived from the corresponding chloroacetylamino acids.[34] Chloro-acetylamino acids would be expected to give unsaturated azlactones as by-products in many mixed anhydride syntheses.[15]

A remarkable reaction discovered by Beecham[16,17] is probably applicable to a variety of α-tosylamino acid mixed anhydrides. He observed that α-tosylamino acid chlorides react with aqueous sodium hydroxide solution with evolution of carbon monoxide (86–99% yields) and the formation of an aldehyde (or ketone), p-toluenesulfonamide, and sodium chloride.

$$p-CH_3C_6H_4SO_2NHC(R_1R_2)COCl + NaOH \rightarrow p-CH_3C_6H_4SO_2\overset{\ominus}{N}CR_1R_2COCl$$
$$\downarrow$$
$$p-CH_3C_6H_4SO_2NH_2 + R_1R_2CO \xleftarrow{H_2O} p-CH_3C_6H_4SO_2N=C(R_1R_2) +$$
$$CO + NaCl + H_2O$$
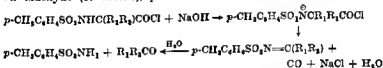
The reaction is slower with sodium carbonate than with sodium hydroxide and fails with sodium bicarbonate. With aqueous ammonia, but not with glycine or proline, a tosylamino acid amide results. α-Tosyl-DL-valyl azide dissolved in aqueous sodium hydroxide with effervescence, and the odor of isobutyraldehyde was noticeable.[18] This suggests that the Beecham reaction may be fairly general for α-tosylamino acid mixed anhydrides.

To avoid the Beecham reaction in the acylation of amino acid salts with α-tosylamino acid alkyl carbonates it is merely necessary to control the pH of the solution by introducing magnesium oxide, sodium bicarbonate, or similarly weak alkaline reagents. However, even under mildly basic conditions α-tosylamino acid alkyl carbonates do not always react smoothly. α-Tosylisoleucine alkyl carbonates give less satisfactory results in peptide synthesis than do carbobenzyloxyisoleucine alkyl carbonates.[18] Various α-tosylalanine phosphate esters in model coupling experiments with cyclohexylamine gave unpromising results (unpublished work, but see ref 19). Protection of the α-amino group by groups other

[34] Kogl and Schouman, *Rec trav chim*, **75**, 29 (1956).
[15] N F Albertson Unpublished results
[16] Beecham, *Chem & Ind (London)*, **36**, 1120 (1955)
[17] Beecham, *J. Am Chem Soc*, **79**, 3257 (1957)
[18] Theodoropoulos and Craig, *J Org Chem*, **21**, 1120 (1956)
[19] Kenner, Khorana, and Stedman, *J. Chem Soc*, **1953**, 673

than tosyl was not investigated. On the other hand, the mixed anhydride of sulfuric acid and tosylglycine of Kenner[5] condensed with phenylalanine in 86% yield and with phenylalanylglycine in 92% yield. This method differs from other mixed anhydride procedures in that the sulfuric acid mixed anhydride III is used in the form of its salt.
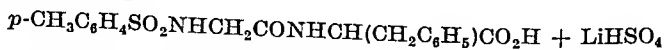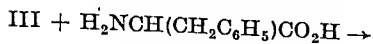
$$p\text{-}CH_3C_6H_4SO_2NHCH_2CO_2Li + SO_3 \rightarrow p\text{-}CH_3C_6H_4SO_2NHCH_2COOSO_3Li$$
$$\text{III}$$

$$\text{III} + H_2NCH(CH_2C_6H_5)CO_2H \rightarrow$$
$$p\text{-}CH_3C_6H_4SO_2NHCH_2CONHCH(CH_2C_6H_5)CO_2H + LiHSO_4$$
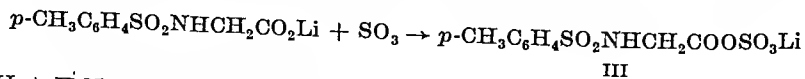
Structure of the Amine. The amine that is acylated may be either the salt or the ester of an amino acid or peptide. If an ester is employed, a neutral product is obtained from which the acidic and basic starting materials may be readily removed by extraction with sodium bicarbonate solution and dilute hydrochloric acid. The use of an alkali metal salt results in the formation of an acidic product which often requires countercurrent distribution to separate it in a pure state from any of the original acylamino acid or peptide.

A number of carbobenzyloxyvaline dipeptides were prepared in one of two ways: (A) the mixed anhydride of carbobenzyloxy-DL-valine and ethyl chloroformate in ether was condensed with the ester of an amino acid and the product saponified with alkali; (B) the same mixed anhydride in dioxane was condensed with the sodium salt of an amino acid. The over-all yields were slightly higher by procedure A.[20] Vaughan and Osato[21] suggest that the lower yields obtained with salts are due to the use of an aqueous medium. Vigorous stirring is advisable when sodium salts are used, particularly if the anhydride was prepared in a water-immiscible solvent.

Davis found it impractical to condense carbobenzyloxy dipeptides with the sodium salt of an amino acid because of difficulties in purification.[20] Part of his difficulty could, however, have been due to the presence of mixtures of stereoisomers since he was working with DL-amino acids.

There are several reasons why it is more satisfactory to condense an acylamino acid with the sodium salt of a dipeptide than to condense the acylated peptide with the amino acid.

1. The sodium salt of the dipeptide will have a higher concentration of free amino groups and consequently will give a better yield of acylated product than the amino acid. At pH 7.4 glycyltryptophan has about twenty times the concentration of free amino groups as tryptophan, and

[20] Davis, *Ann. chim. (Paris)*, **9**, 399 (1954).
[21] Vaughan and Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

the peptide reacts more smoothly with silver phenyl carbobenzyloxy-glycylphosphate than tryptophan.[22]

2 The separation of an acyl tripeptide from an α-acylamino acid will generally be easier than the separation of an acyl tripeptide from an acyldipeptide

3. In condensing the carbobenzyloxy or phthaloyl derivatives of the α-acylamino acid with the dipeptide, less racemization would be expected than in condensing the acylated dipeptide with the amino acid. Tri- and higher peptides, however, are more susceptible to racemization than dipeptides, and methods avoiding alkaline solution are usually necessary to retain optical purity.

If the ester of an amino acid or peptide is used as the amine component, the ester group must ultimately be removed. Although saponification is commonly employed, the ester group may be removed without recourse to alkaline media. Esters such as methyl and ethyl will undergo hydrolysis in aqueous hydrochloric or hydrobromic acid, and esters such as benzyl, t-butyl, and cyclopentyl will undergo alkyl-oxygen fission with anhydrous halogen acids.[25-28] Benzyl esters are also converted to the acids by hydrogenolysis.[29]

Several instances have been cited where a mixed α-acylamino anhydride will react with the ester of an amino acid and not with the sodium salt, or vice versa Thus the mixed anhydride from trityIglycine and ethyl chloroformate reacts with ethyl glycinate to give ethyl trityIglycylglycin-ate in 63% yield, but the same anhydride does not react with an aqueous dioxane solution of sodium glycinate to give the trityldipeptide.[8] The acid chloride of L-3-formyl-2,2-dimethylthiazolidine-4-carboxylic acid could not be formed, but the mixed anhydride with carbonic acid acylated methyl glycinate in the normal manner[21] but failed to acylate sodium glycinate.[31] The mixed anhydride of formylglycine and ethyl chloroformate acylated p-aminobenzoic acid in 47% yield but reacted with ethyl p-aminobenzoate to give the urethan in 55% yield.[12] These results were attributed to the abnormal behavior of the mixed anhydride in yielding

[23] Hartzusne Biochem J and Biophys Acta, 4, 484 (1950)
[24] Anderson, J Am Chem Soc 75, 6081 (1953),
[25] Sheehan, Chapman, and Roth, J Am Chem Soc, 74, 3822 (1952);
[26] Ben Ishai, J Org Chem, 18, 62 (1954)
[27] Ben Ishai and Berger, J Org Chem, 17, 1564 (1952)
[28] Sheehan and Laubach, J Am Chem Soc, 73, 4752 (1951)
[29] McKay and Albertson, J Am Chem Soc, 79, 4686 (1957)
[30] Anderson and Callahan, J Am Chem Soc, 82, 3359 (1960)
[31] King, Clark Lewis, and Wade, J Chem Soc, 1957, 880
[32] Sheehan and Yang, J Am Chem Soc, 80, 1158 (1958)

King, Clark Lewis, and Wade, in Adams, Organic Reactions, Vol 7, p 263, John Wiley & Sons
New York, 1953

the cation $C_2H_5O_2C^{\oplus}$ instead of the expected cation $HCONHCH_2CO^{\ominus}$. The assumption that the reaction proceeds through an acyl carbonium intermediate does not explain its abnormal course. The solvent may play an important role in determining which way a mixed anhydride will react.[3, 4, 6]

Racemization

Greenstein[33] has calculated the probability that all the amino acid residues in a peptide of n residues are of a single optical configuration when the starting material is of various degrees of optical purity. For a decapeptide, the probability is 0.90 if 1% of optical enantiomorph is present in each starting amino acid, and 0.35 if 10% of enantiomorph is present. Since racemization likewise leads to introduction of the optical enantiomorph, it is apparent that even 5% racemization at each step is intolerable for the synthesis of higher peptides.

Compounds that possess the structural unit —CONHCHRCOX may undergo racemization as shown below.
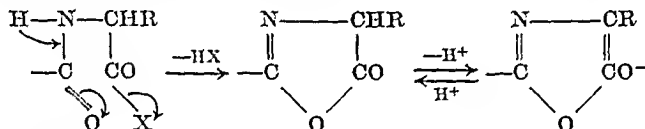
Racemization of α-acylamino acids via mixed anhydrides (of acetic acid) and azlactones (oxazolones) has been reviewed.[34] The nature of X has a considerable influence on the extent of racemization, but data are not available to make a comparison among the various anhydrides. The azide ($X = N_3$) is remarkably resistant to racemization,[35,36] and it is probably unique among mixed anhydrides in this respect. Thiol esters are relatively resistant to attack by alkoxide ion but are readily aminolyzed. Thus carbobenzyloxyglycyl-L-leucyl thiophenolate and sodium glycinate in aqueous tetrahydrofuran gave the carbobenzyloxy tripeptide with retention of activity in 70% yield.[37] However, the p-nitrophenyl thiol ester of carbobenzyloxyglycyl-L-alanine reacted with L-phenylalanylglycine in aqueous dioxane to give a product containing 70% of the LL form and 30% of the DL form.[38]

Amino acids other than serine, threonine, or cysteine in which the amino group is protected by a carbalkoxy, phthaloyl, p-toluenesulfonyl,

[33] Greenstein, in *Advances in Protein Chemistry*, Vol. 9, p. 190, Academic Press, New York. 1954.

[34] Neuberger, in *Advances in Protein Chemistry*, Vol. 4. p. 356, Academic Press. New York. 1948.

[35] North and Young. *Chem. & Ind. (London).* 1955, 1597.

[36] Springall, *Nature*, 175, 1117 (1955).

[37] Wieland and Heinke, *Ann.*, 615, 184 (1958).

[38] Farrington, Hextall, Kenner, and Turner, *J. Chem. Soc.*, 1957, 1407.

or trityl groups are generally not subject to racemization. However, all acyl peptides except those with a terminal carboxy group in a glycine, proline, or hydroxyproline residue may be racemized during anhydride formation In the ethyl ester of carbobenzyloxy D-serylglycyl-L-alanine, the seryl residue is almost completely racemized in aqueous methanol in the presence of triethylamine at room temperature.[39]

The rate of racemization usually increases as the time and temperature for anhydride formation are increased, but the most important factor is the nature of the solvent. Racemization is reduced in non-polar solvents and in the absence of base.[5] With α-acylaminoacyl alkyl carbonates, tetrahydrofuran and toluene are particularly good solvents for diminishing the rate of racemization whereas chloroform[40] and dimethylformemide[41] are poor in this respect. Chloroform and dimethylformamide may dissolve the triethylamine hydrochloride formed during the preparation of the anhydride, and this salt may influence the rate of racemization If this assumption is correct, tributylamine hydrochloride, which is soluble in many organic solvents, should increase the rate of racemization with benzene as the solvent. If the triethylamine hydrochloride is a major factor in causing racemization, it may prove advantageous to choose a different tertiary amine, or to select a different method of removing hydrogen chloride from the reaction mixture. The free base, or a salt of the α-amino acid ester other than the hydrochloride, might be used.

Several physical methods have been utilized to determine the extent of racemization   Acetyl-L-leucine has been coupled with ethyl glycinate by a variety of procedures[35] Because the optically pure product has a relatively high rotation, rotation can be used as a criterion of purity. A test that permits detection of less than 0 5% racemization involves the acylation of ethyl glycinate with carbobenzyloxyglycyl-L-phenylalanine and subsequent fractional crystallization of the product.[42] Counter-current distribution may be used to separate the optical isomers[32]

Enzymic methods have proved quite satisfactory for detecting racemization   The enzymes used are specific for hydrolysis of peptide bonds in which the newly liberated carboxyl groups are associated with α-amino acid residues of the L configuration of the L configuration. Histidylphenylalanarginyl-tryptophylglycine was synthesized from L-amino acids using N,N'-dicyclohexylcarbodiimide for the coupling reagent.[44]   Treatment of

[39] Schnabel, Z physiol Chem , Hoppe-Seyler s, 314, 114 (1959)
[40] Vaughan, J Am Chem Soc , 76, 6137 (1952)
[41] Vaughan, 128th Am Chem Soc Meeting, Minneapolis, Minn , Sept 1955, Abstracts, p 27c
[42] Anderson and Young, J Am Chem Soc , 74, 5307 (1952)
[43] Schwarz and Bumpus, J Am Chem Soc , 81, 890 (1959)
[44] Hofmann, Woolner, Spuhler, and Schwartz, J Am Chem Soc , 80, 1486 (1958).

pentapeptide with trypsin resulted in the formation of histidylphenyl-alanylarginine and tryptophylglycine together with much unhydrolyzed material as shown by paper chromatograms. Only 37% of the penta-peptide was cleaved. The enzyme leucine aminopeptidase gave histidine, phenylalanine, arginine, tryptophan, and glycine in the molar ratios 1:1:0.4:0.4:0.4. Thus both enzymic methods indicated that only about 40% of the all-L isomer was present. Leucine aminopeptidase was also used to demonstrate that the octapeptide occupying positions 6 to 13 of the ACTH molecule has been synthesized without racemization.[45]

The optical purity of eight tripeptides of D- and L-valine, prepared by the dicyclohexylcarbodiimide procedure, was demonstrated through the use of a microbiological assay for L-valine.[46]

Racemization can be avoided by condensing a carbalkyloxy (or phthaloyl, tosyl, or trityl)amino acid with a peptide so as to lengthen the chain by one amino acid at a time. By this method histidylphenyl-alanylarginyltryptophylglycine was synthesized using dicyclohexyl-carbodiimide to form most of the peptide bonds.[47] The product was completely hydrolyzed by trypsin to histidylphenylalanylarginine and tryptophylglycine; chymotrypsin gave histidylphenylalanine, arginyl-tryptophan, and glycine.

Coupling of larger peptide fragments at a glycine or proline residue, or synthesis through the azide, also avoids racemization.

No systematic study of the effect of the α-amino acid side chain on the rate of racemization has appeared.

BIS-(α-ACYLAMINOACYL)CARBONATES

Carbobenzyloxyglycine reacts with phosgene in the presence of a tertiary base in an inert solvent to give a mixed anhydride which, when condensed with glycine, gave carbobenzyloxyglycylglycine in 40% over-all yield.[48] The proposed pathway is shown in the accompanying equations.

$$2C_6H_5CH_2OCONHCH_2CO_2H + 2NR_3 + COCl_2 \rightarrow$$
$$(C_6H_5CH_2OCONHCH_2COO)_2CO + 2R_3NHCl$$
$$\text{IV}$$

$$\text{IV} \rightarrow (C_6H_5CH_2OCONHCH_2CO)_2O + CO_2$$
$$\downarrow H_2NCH_2CO_2H$$

$$C_6H_5CH_2OCONHCH_2CONHCH_2CO_2H + C_6H_5CH_2OCONHCH_2CO_2H$$
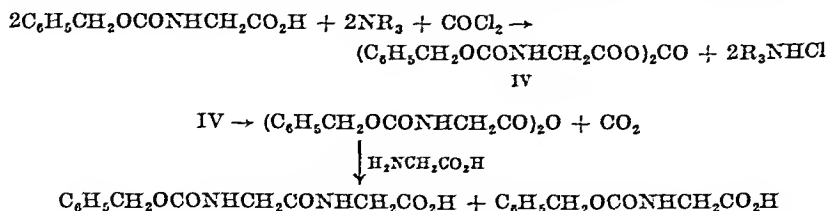
[45] Boissonnas, Guttmann, Huguenin, Jaguenoud, and Sandrin, *Helv. Chim. Acta*, **41**, 1867 (1958).

[46] Schankman and Schvo, *J. Am. Chem. Soc.*, **80**, 1164 (1958).

[47] Schwyzer and Li, *Nature*, **182**, 1669 (1958).

[48] Wieland and Bernhard, *Ann*, **572**, 190 (1951).

The yields could possibly be improved by operating at temperatures below zero, but the method would still be less convenient than others that are available

α-ACYLAMINOACYL CHLOROCARBONATES

A mixed anhydride of N-benzyl-DL-aspartic acid and phosgene was reported to have the structure V [49] This proposed structure seems open

$$
\begin{array}{c}
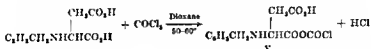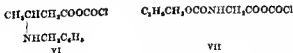CH_2CO_2H \\
| \\
C_6H_5CH_2NHCHCO_2H
\end{array}
+ COCl_2 \xrightarrow[50-60°]{Dioxane}
\begin{array}{c}
CH_2CO_2H \\
| \\
C_6H_5CH_2NHCHCOOCOCl
\end{array}
+ HCl
$$
$$
V
$$

to considerable doubt since its formation would imply that (1) a basic amine fails to react with the hydrogen chloride which is formed as a by-product, (2) the amino group is not acylated by an active acylating group in the same molecule, (3) excess phosgene fails to react with an available carboxyl group, and (4) both an acid and an anhydride coexist without reacting to liberate hydrogen chloride even though a base is present and the reaction product is in solution. The presumed mixed anhydride has been used to prepare both alpha and beta amides[50] and peptides [49, 51]

Reaction of N,benzyl-DL-β-aminobutyric acid with phosgene in dioxane at 60° was reported to give the mixed anhydride VI [51] This structure is unlikely for some of the reasons just cited against the formation of a compound of structure V.

$$
\begin{array}{c}
CH_3CHCH_2COOCOCl \\
| \\
NHCH_2C_6H_5
\end{array}
$$
$$
VII
$$

$$C_6H_5CH_2OCONHCH_2COOCOCl$$
$$VII$$

Carbobenzyloxylglycine reacts with phosgene at −70° to give the mixed anhydride VII This decomposes at −5° to give the symmetrical carbobenzyloxyglycine anhydride However, at −70° in pyridine carbobenzyloxyglycyl chlorocarbonate (VII) is more stable and has been used to acylate a phenolic hydroxyl group [53] Presumably peptide syntheses could also be carried out at −70°

[49] Liwschitz and Zilkha, *J Am Chem Soc*, **76**, 3698 (1954)

[50] Liwschitz, Edlitz Pfeffermann, and Lapidoth, *J. Am Chem Soc*, **78**, 3069 (1956)

[51] Liwschitz and Zilkha, *J Am Chem Soc*, **1957**, 4394.

[52] Zilkha and Rivlin, *J Org Chem*, **22**, 94 (1958)

[53] Brenner, Zimmermann, Quitt, Schneider, and Hartmann, *Helv Chim Acta*, **40**, 604 (1957).

α-ACYLAMINOACYL ALKYL CARBONATES

The most widely used of the newer synthetic methods for forming a peptide bond involves a mixed carbonic-carboxylic acid anhydride and was developed in 1951 simultaneously in three different laboratories.[48, 54–56] Essentially the method consists of the formation of a mixed anhydride by the reaction of a tertiary amine salt of an α-acylamino acid or peptide with an alkyl chloroformate in an indifferent solvent at a low temperature. To this solution of mixed anhydride the amino acid or peptide ester that is to be acylated is then added. Isolation of the mixed anhydride is not necessary or even desirable, although it may be separated from the by-product ammonium salt. Thus treatment of dicarbobenzyloxy-L-lysine in toluene with triethylamine and isobutyl chloroformate gives the mixed anhydride VIII which reacts with ethyl valinate to give ethyl dicarbo-benzyloxy-L-lysyl-L-valinate in 81% yield.[57]

$$\text{CbzoNH(CH}_2)_4\text{CH(NHCbzo)CO}_2\text{H} + (\text{C}_2\text{H}_5)_3\text{N} + \text{ClCO}_2\text{C}_4\text{H}_9\text{-}i \rightarrow$$

(Cbzo = C$_6$H$_5$CH$_2$OCO—)

$$\text{CbzoNH(CH}_2)_4\text{CH(NHCbzo)COOCO}_2\text{C}_4\text{H}_9\text{-}i + (\text{C}_2\text{H}_5)_3\text{NHCl}$$
$$\text{VIII}$$

$$\text{VIII} + (\text{CH}_3)_2\text{CHCH(NH}_2)\text{CO}_2\text{C}_2\text{H}_5 \rightarrow$$
$$\text{CbzoNH(CH}_2)_4\text{CH(NHCbzo)CONHCHCO}_2\text{C}_2\text{H}_5 + \text{CO}_2 + i\text{-C}_4\text{H}_9\text{OH}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad | $$
$$\qquad\qquad\qquad\qquad\qquad\qquad\text{CH(CH}_3)_2$$

The appeal of this method comes from the facts that it employs readily available reagents, is simple and rapid, may be run at low temperatures, and gives by-products that are ordinarily easy to separate.

Scope and Limitations

The Amine Component. Any amino acid or peptide derivative having a free primary amino group may serve as the amine component. Secondary amines tend to react to give urethans. Poor results have been obtained in the acylation of sarcosine[58] and proline (both the acid and the ethyl ester),[59] and in the preparation of other N-substituted peptide linkages. However, in certain cases proline gives good results. Thus carbobenzyloxy-L-alanyl-L-phenylalanine, after conversion to the mixed carbonic anhydride, coupled with methyl L-prolyl-L-leucinate in 79% yield.[60]

[54] Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).

[55] Boissonnas, *Angew. Chem.*, **63**, 194 (1951).

[56] Vaughan, *J. Am. Chem. Soc.*, **73**, 3547 (1951).

[57] Vaughan and Eichler, *J. Am. Chem. Soc.*, **75**, 5556 (1953).

[58] Leister and Tarbell, *J. Org. Chem.*, **23**, 1152 (1958).

[59] Rydon and Smith, *J. Chem. Soc.*, **1956**, 3642.

[60] Oertel, *Angew. Chem.*, **70**, 51 (1958).

The copper complex of lysine has been used to protect the α-amino group, while the ε-amino group was acylated by carbobenzyloxyamino acid ethyl carbonates [61]

The synthesis of peptide intermediates in which a hydroxy amino acid is the amine component usually presents no special difficulties. However, the use of 2 moles of serine per mole of mixed anhydride is recommended to minimize side reactions with the hydroxyl group.[31] O-Acyl derivatives of serine which are of interest in the synthesis of azaserine may be prepared from a carbonic acid mixed anhydride and an N-protected serine.[62-64] The reaction of tritylglycine with N-trityl-DL-serine gives a quantitative yield of crude O-(N-tritylglycyl)-N-trityl-DL-serine.[62]

When the protecting groups are removed from peptide intermediates, acyl migration from oxygen to nitrogen (or vice versa) may occur when non N-terminal seryl or threonyl residues are present.[65] An example is shown in the accompanying reaction. An observation in this laboratory

$$H_2NCHRCOOCH_2CH(NH_2)CO_2H \underset{\text{Acid}}{\overset{\text{Base}}{\rightleftharpoons}} H_2NCHRCONHCH(CH_2OH)CO_2H$$

regarding this well-known reaction deserves comment. When an N-carbobenzyloxyaminoacyl serine or threonine is treated with hydrogen bromide in nitromethane,[65] the N-dipeptide hydrobromide usually precipitates as soon as it is formed and prevents rearrangement to the O-dipeptide. On the other hand, the use of hydrogen bromide in glacial acetic acid[34] results in rearrangement and the O-dipeptide may be isolated. To avoid the risk of deamidation of asparagine or glutamine peptides in a subsequent ester saponification, the sodium salt of asparagine or glutamine may be used in place of the corresponding ester in the synthesis although the yields of product are then lower.[66]

Neutral Amino Acids. Glycine, alanine, valine, leucine, isoleucine, methionine, S-benzylcysteine, proline, phenylalanine, and tryptophan present no special difficulties in this reaction. Yields of recrystallized materials are usually about 70-80% Carbobenzyloxy-D-alanine, however, as the mixed anhydride with isobutyl chloroformate reacts with ethyl L-alaninate to form a dipeptide intermediate in only a very low yield.[67] Halogenated, nitrated, unsaturated, or otherwise modified neutral amino acids may be employed. It is not necessary for the amine

[61] Theodoropoulos, *J Org Chem.*, **22**, 140 (1958)

[62] Moore, Dice, Nicolaides, Westland, and Wittle, *J Am Chem Soc.*, **76**, 2884, 2887 (1954)

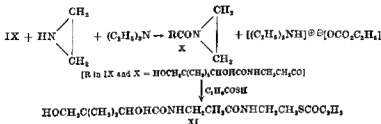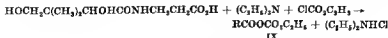[63] Velluz, Amiard, and Heymes, *Bull soc chim France*, 1955, 1283

[64] Australian pat appl 18508/53 (in Parke, Davis)

[65] Albertson and McKay, *J Am Chem Soc.*, **75**, 6323 (1953).

[66] Leach and Lindley, *Australian J Chem.*, **7**, 173 (1954) [*O A*, **49**, 6832 (1955)].

[67] Fu, Birnbaum, and Greenstein, *J Am Chem Soc.*, **76**, 6054 (1954)

Mixed carbonic anhydrides of pantothenic acid have been used to form amides.[73-77] These mixed anhydrides illustrate a type in which the acid contains primary and secondary hydroxyl groups. Of particular interest is the synthesis of benzoylpantethein.[78, 79] The mixed anhydride IX of triethylammonium pantothenate and ethyl chlorocarbonate reacts with ethylene imine to form pantothenyl ethylene imine (X), which is converted by means of thiobenzoic acid to benzoylpantethein (XI).

$$HOCH_2C(CH_3)_2CHOHCONHCH_2CH_2CO_2H + (C_2H_5)_3N + ClCO_2C_2H_5 \rightarrow$$
$$RCOOC_2C_5H_4 + (C_2H_5)_3NHCl$$
$$\hspace{3cm} IX$$

$$\hspace{2cm} CH_2$$
$$IX + HN\ \ | \ \ + (C_2H_5)_3N \rightarrow RCON\ \ | \ \ + [(C_2H_5)_3NH]^{\oplus} {}^{\ominus}[OCO_2C_2H_5]$$
$$\hspace{2cm} CH_2 \hspace{3.5cm} CH_2$$
$$\hspace{1cm} X$$

[R in IX and X = $HOCH_2C(CH_3)_2CHOHCONHCH_2CH_2CO$]

$$\hspace{4cm} C_6H_5COSH$$

$$HOCH_2C(CH_3)_2CHOHCONHCH_2CH_2CONHCH_2CH_2SCOC_6H_5$$
$$\hspace{4cm} XI$$

Tyrosine. The presence of a phenolic group in the acid usually interferes with mixed anhydride formation since the phenolic group reacts with the alkyl chloroformate.[80] One example,[79] salicylic acid provides one example,[79] and carbobenzyloxytyrosine another.[80] It is necessary to block the phenolic group in tyrosine to obtain satisfactory results;[81] tosyl,[81] carbobenzyloxy,[82] and acetyl[83] derivatives have been used. On the other hand, no blocking is necessary with carbobenzyloxy-L-seryl-L-tyrosine. The mixed anhydride with ethyl chloroformate is formed, and it couples with the methyl esters of leucine, valine, phenylalanine,[83] or isoleucine[84] in 60–75% yields. Likewise, both N-tosyl-S-benzyl-L-cysteinyl-L-tyrosine[85] and N-carbobenzyloxy-S-benzyl L-cysteinyl-L-tyrosine[82] react as the anhydride with isobutyl chloroformate with

[73] Wieland and Bokelmann, *Naturwiss.*, **33**, 384 (1951)
[74] Schwyzer, *Helv. Chim. Acta*, **35**, 1903 (1952)
[75] Boehringer et al., Brit pat 707,709 (to Boehringer Sohn) [C A. 50, 4202a (1956)]
[76] Felder and Pitre, *Angew Chem*, **68**, 735 (1956)
[77] Same pat 305,261 (to Boehringer Sohn) (Chem. Zentr., 127, 14574 (1956))
[78] Belg pat 521,193 (to Ciba) (1953)
[79] Ger pat 117,267 (to Knoll and Co) [*Friedländer*, **6**, 146 (1900–1902)]
[80] Akimova and Gavrilov, *Zhur Obshchei Khim*, **24**, 381 (1954) [C A. 49, 4519f (1955)]
[81] Katsoyannis, Gish, and du Vigneaud, *J Am Chem Soc*, **79**, 4516 (1957).
[82] Katsoyannis and du Vigneaud, *J Am Chem Soc*, **78**, 4482 (1956)
[83] Boissonnas, Guttmann, Jaquenoud, and Waller, *Helv Chim Acta*, **39**, 1421 (1956)
[84] Boissonnas, Guttmann, Jaquenoud, and Waller, *Helv Chim Acta*, **38**, 1491 (1955)
[85] du Vigneaud, Bartlett, and Johl, *J Am Chem Soc*, **79**, 5572 (1957)
[86] du Vigneaud, Gish, and Katsoyannis, *J Am Chem Soc*, **76**, 4751 (1954).

L-phenylalanyl-L-glutaminyl-L-asparagine to give 62–64% yields of crude product. The analogous anhydride of N-tosyl-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanine gives the peptide with L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteine in 59% yield.[87] Because the presence of S-benzyl-L-cysteine adjacent to the tyrosine residue may reduce the reactivity of the phenolic hydroxyl group, it is unnecessary to protect it.

Basic Amino Acids. If both amino groups of lysine are protected, there is no difficulty in coupling lysine through a mixed anhydride with other amino acids. The use of α-N-carbobenzyloxy-*im*-benzyl-L-histidine* failed because of the insolubility of its triethylammonium salt.[88] However, with the same base dicarbobenzyloxy-L-histidine[89,90] and dicarbocyclopentyloxy-L-histidine gave the mixed anhydride.[15]

Blocking the guanido group of arginine through formation of the ω-nitro derivative permits the formation of α-N-carbobenzyloxy-ω-nitro L-arginyl ethyl carbonate with no difficulty.[91] The hydrazide or acid chloride could not be prepared from α-N-carbobenzyloxy-ω-nitro-L-arginine.[1] The mixed anhydride of α-N-*p*-nitrocarbobenzyloxy-ω-nitro-L-arginine and ethyl chlorocarbonate has also been used to prepare arginine peptides.[92]

The protection of the guanido group of arginine by percarbobenzyloxylation has recently been accomplished.[93,94] The resulting tricarbobenzyloxy-L-arginine (precise structure unknown) was converted to the mixed anhydride with ethyl chloroformate and used for peptide syntheses. Benzyl tricarbobenzyloxy-L-arginyl-ω-N-carbobenzyloxy-L-argininate was prepared in 73% yield, but for its isolation it was necessary to wash with aqueous triethylamine to remove tricarbobenzyloxy-L-arginine, rather than with aqueous carbonate or bicarbonate because of the high solubility of the sodium or potassium salts of tricarbobenzyloxy-L-arginine in chloroform and the relatively low solubility in water.

The use of the mixed carbonic anhydride of guanidoacetic acid to prepare the peptide XII in 10% yield has been reported.[95]

[87] Katsoyannis, Gish, Hess, and du Vigneaud, *J. Am. Chem. Soc.*, **80**, 2558 (1958).

* The prefix *im* indicates substitution on the imidazole ring. The convention follows the nomenclature suggested by Wieland in ref. 229 (see p. 208).

[88] Winterstein, Hegedus, Fust, Böhni, and Studer, *Helv. Chim. Acta*, **39**, 233 (1956).

[89] Akabori, Okawa, and Sakiyama, *Nature*, **181**, 772 (1958).

[90] Patchornik, Berger, and Katchalski, *J. Am. Chem. Soc.*, **79**, 6416 (1957).
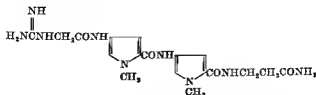
[91] Hofmann, Rheiner, and Peckham, *J. Am. Chem. Soc.*, **75**, 6083 (1953).

[92] Berse and Piche, *J. Org. Chem.*, **21**, 808 (1956).

[93] Zervas, Winitz, and Greenstein, *Arch. Biochem. Biophys.*, **65**, 573 (1956).

[94] Zervas, Winitz, and Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

[95] Weiss, Webb, and Smith, *J. Am. Chem. Soc.*, **79**, 1266 (1957).

NH
|
$H_2NCNHCH·CONH$

XII

Acidic Amino Acids and Their Amides. Conflicting claims appear in the early literature dealing with aspartic and glutamic acid peptides. The newer techniques of paper chromatography and countercurrent distribution show that when it is possible for a reaction to proceed by way of an acylglutamic acid anhydride or imide a mixture of products will be obtained, although either the α or ω isomer may predominate.[96-99] Even the reaction of the azide derived from carbobenzoxy-L-glutamic acid-γ-hydrazide with amino acid esters leads to a mixture of isomers.[98, 100] The mixed carbonic carboxylic anhydride method, however, applied to mono esters of acyl-L-glutamic acids gives homogeneous products.[96, 97, 101, 102]

It has been suggested that where yield is not an important factor peptides of acylglutamic acids may be conveniently prepared by the use of *one* equivalent of both ethyl chloroformate and triethylamine. The mixture of α and γ peptides which results may be separated by countercurrent distribution or by fractional extraction or precipitation.

Acylglutamic acid amides of structure XIII were readily cyclized to the imide XIV with thionyl chloride and pyridine. Dilute alkali converts the imide XIV to the isomeric acids XV. Ring opening of XIV in the opposite direction occurs if the R_1CO group is replaced by a trityl group. This may be due to steric factors. Thus diethyl trityl-L-glutamyl-glycine gives, on saponification, trityl-α-L-glutamylglycine.[103, 104] With thionyl chloride at 0°, N-benzoyl-α-DL-glutamylglycine n-hexylamide (XIII, $R_1 = C_6H_5$, $R_2 = CH_2CONHC_6H_{13}$-n) cyclized to the acylpyrrolidone XVI, whereas the corresponding mixed carbonic anhydride cyclized

---

[96] Sachs and Brand, *J. Am. Chem. Soc.* **75**, 4608 (1953).

[97] Sachs and Brand, *J. Am. Chem. Soc.* **76**, 1811 (1954).

[98] Sachs and Brand, *J. Am. Chem. Soc.* **76**, 1815 (1954).

[99] Wieland and Weidenmüller, *Ann.*, **597**, 181 (1955).

[100] Bruckner, Kajtár, Kovács, Nagy, and Wein, *Tetrahedron*, **2**, 216 (1958).
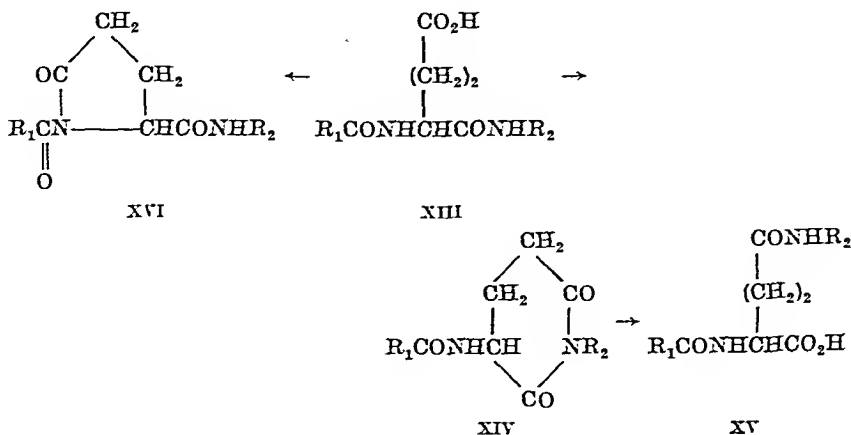
[101] Battersby and Robinson, *J. Chem. Soc.*, **1955**, 259.

[102] Kraml and Bonthellier, *Can. J. Chem.*, **33**, 1630 (1955).

[103] Amiard, Heymès, and Vellus, *Bull. soc. chim. France*, **1956**, 97.

[104] Amiard, Heymès, and Vellus, *Fr. pat* **1,129,627** [*Chem. Zentr.* **130**, 625 (1959)].

in the opposite direction to give DL-α-benzamidoglutaroylglycine n-hexylamide (XIV; $R_1 = C_6H_5$, $R_2 = CH_2CONHC_6H_{13}$-n).[105]

The acyl isoglutamine derivatives XIII cyclize "extremely easily" to the imides XIV,[5] for example with acetic anhydride.[106] Hydrolysis of the imides XIV leads to mixtures of isomeric acids XIII and XV.[101,105] Such results support the statement that glutamine gives unsatisfactory results with the alkyl carbonic anhydride method.[41] However, the ethyl chloroformate mixed anhydride of carbobenzyloxy-L-glutamine couples with L-asparaginyl-S-benzyl-L-cysteine methyl ester to give a 72% yield of product[84] and with other amino acid and peptide esters in yields of 56–63%.[83] The first coupling reaction was carried out also with the anhydride from sec-butyl chloroformate.[107]

Results with aspartic acid parallel those with glutamic acid. Both the acyl anhydride[108] and the imide[84,101,109] of aspartic acid may open to give a mixture of α and β isomers; consequently syntheses must be designed to avoid these intermediates. The mono ester of an acylaspartic acid can be used for the synthesis of peptides. The resulting β-alkyl acylaspartyl peptide, however, is very unstable to alkali and is readily converted to the corresponding imide.[101] Benzoyl-L-isoasparagine ethyl ester (XVII) was converted through the intermediate imide XVIII to a mixture of benzoyl-L-asparagine (XIX) and benzoyl-L-isoasparagine (XX)

[105] Battersby and Robinson, J. Chem. Soc., 1956, 2076.

[106] Kováks, Medzihradszky, and Bruckner, Acta Chim. Acad. Sci. Hung., 6, 183 (1955) [C.A., 50, 11245 (1956)].

[107] Rudinger, Honzl, and Zaoral, Collection Czechoslov. Chem. Communs., 21, 202 (1956). Published in Czech. in Chem. Listy., 50, 288 (1956) [C.A., 50, 12826 (1956)].

[108] LeQuesne and Young, J. Chem. Soc., 1952, 24.

[109] Sondheimer and Holley, Nature, 173, 773 (1954); cf. J. Am. Chem. Soc., 76, 2467 (1954).

by the use of either aqueous sodium hydroxide or warm 0.2N aqueous sodium carbonate It is apparent that the coupling of an acylaspartic

$$C_6H_5CONHCHCONH_2 \rightarrow \left[C_6H_5CONHCHCONH \atop CH_2CO_2C_2H_5 \right]$$

$$C_6H_5CONHCHCO_2H \quad C_6H_5CONHCHCONH_2 \quad C_6H_5CONHCHCO$$

$$CH_2CONH_2 \quad CH_2CO_2H \leftarrow \quad CH_2CO$$

XIX   XX   XVIII
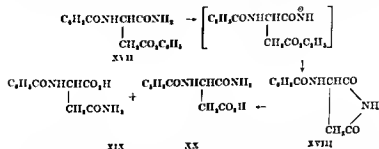
or acylglutamic acid with an amino acid or peptide in basic solution by any anhydride procedure may lead to rearranged products. If the coupling with an amino acid ester or peptide ester is performed in neutral solution, the normal product may be expected. However, saponification of ester groups may be accompanied by rearrangement.

The mixed carbonic anhydride procedure has failed for some workers[66] for the preparation of asparaginyl peptides, whereas others have reported successful results with yields up to about 50%. The carbobenzyloxy-L-asparagine mixed anhydride with ethyl chloroformate has been coupled with methyl L-serinate in 22% yield and with ethyl L-serylglycinate in 9% yield.[110] Carbobenzyloxy-L-asparagunyl-S-benzyl-L-cysteine methyl ester was prepared in essentially the same yield by the mixed carbonate (52%) and phosphorazo* method (56%) The carbobenzyloxy-L-glutamyl-L-asparagine mixed anhydride with sec-butyl chloroformate was coupled with S-benzyl-L-cysteine methyl ester in 47% yield.[107] With the latter two peptides it has been shown that dehydration of the amide bond of asparagine to the nitrile occurs to an appreciable extent when the pyrophosphite or dicyclohexylcarbodiimide method is employed, but it is not observed with the mixed carbonic anhydride procedure.

Side Reactions

Disproportionation. The first side reaction observed in the use of mixed anhydrides of α-acylamino acids and alkyl carbonates was disproportionation.[45] Since the symmetrical anhydride can acylate only

$$2R_1CONHCHR_2COOCO_2R_3 \rightarrow (R_1CONHCHR_2CO)_2O + (R_3O)_2CO + CO_2$$
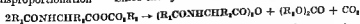
half as much amine as can the mixed carbonic anhydride, disproportion-

[110] Fischer and Whetstone, J Am Chem Soc 77, 750 (1955)

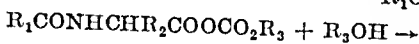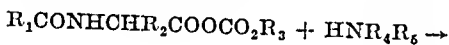* The phosphorazo method was developed by Goldschmidt and co-workers See Angew. Chem, 62, 538 (1950), Ann 533, 68 (1953)

tion obviously results in decreased yield. Disproportionation is favored by a long reaction time in the anhydride-forming step. Carbobenzyloxyglycylglycine was converted to carbobenzyloxyglycylglycine anhydride when it was allowed to react for 65 minutes with benzyl chloroformate in diethylformamide, but gave the mixed anhydride when the reaction time was decreased to 5 minutes.[111] Low reaction temperatures lessen disproportionation.[48] It has been suggested that liberation of carbon dioxide during the preparation of the mixed anhydride indicates disproportionation, but this is not always true since carbon dioxide is also a by-product of a modified Dakin-West reaction as noted in the next section.

Ester Formation. In some reactions esters were isolated as by-products when acylamino carboxylic alkyl carbonates were employed to acylate amines. The esters were considered to have been formed by the loss of carbon dioxide from the mixed anhydride.[41]

$$R_1CONHCHR_2COOCO_2R_3 \rightarrow R_1CONHCHR_2CO_2R_3 + CO_2$$
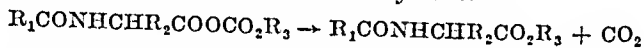
An alternative explanation would be that the mixed anhydride reacts with the alcohol liberated during amide formation. However, the formation of esters in the presence of a primary or secondary amine by acylation of alcohols formed as by-products could not account for any great amount of ester formation.

$$R_1CONHCHR_2COOCO_2R_3 + HNR_4R_5 \rightarrow$$
$$R_1CONHCHR_2CONR_4R_5 + R_3OH + CO_2$$
$$R_1CONHCHR_2COOCO_2R_3 + R_3OH \rightarrow$$
$$R_1CONHCHR_2CO_2R_3 + R_3OH + CO_2$$
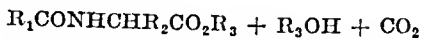
Where azlactone formation is possible, another pathway for ester formation is open. Hippuric acid reacts with ethyl chloroformate in the presence of triethylamine to give ethyl hippurate and carbon dioxide. Since, in the presence of benzaldehyde at 0°, 2-phenyl-4-benzylidenoxazol-5-one was obtained in 11% yield in addition to ethyl hippurate, the reaction was assumed to proceed via the mixed carbonic anhydride XXI and the azlactone XXII.[112] In this instance no amine was present to react with the mixed anhydride. (See equations on p. 181.)

Still another method of formation of esters is possible. The addition of the sodium salt or ester of an amino acid to the mixed anhydride formed from phenylacetic acid and isobutyl chloroformate failed to result in any amide formation but gave instead an excellent yield of isobutyl phenylacetate.[113] This product may be explained as the result
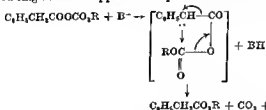
[111] von Brunn-Leube and Schramm, *Chem. Ber.*, 89, 2045 (1956).
[112] Swan, *Australian J. Sci. Research, Ser. A*, 5, 728 (1952).
[113] R. L. Perry and N. F. Albertson. Unpublished results.

$$[C_6H_5CONCHCH_2CO_2]^{\ominus}[NH(C_2H_5)_3]^{\oplus} + ClCO_2C_2H_5 \rightarrow$$
$$C_6H_5CONCHCH_2COOCO_2C_2H_5 + (C_2H_5)_3NHCl$$
$$XXI$$

$$\downarrow$$

$$C_6H_5CONCHCH_2CO_2C_2H_5 + \begin{array}{c} H_2C—CO \\ \diagdown \diagup \\ N \quad O \\ \diagdown C \diagup \\ \| \\ O \\ XXII \end{array} + C_2H_5OH + CO_2$$
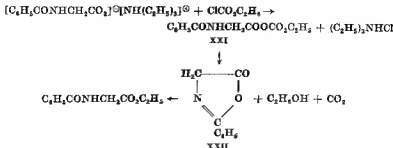
of a modified Dakin-West reaction in which an ester is formed instead of a ketone. The general mechanism proposed by King and McMillan for the Dakin-West reaction[124, 125] readily accommodates this extension of the reaction, although an intramolecular reaction involving a four-membered ring as shown appears more plausible

$$C_6H_5CH_2COOCO_2R + B^- \rightarrow \begin{bmatrix} C_6H_5CH\!-\!CO \\ \diagdown \diagup \\ ROC\!\!-\!\!O \\ \| \\ O \end{bmatrix} + BH$$

$$\downarrow$$

$$C_6H_5CH_2CO_2R + CO_2 + B^-$$

Diphenylacetic acid, which does not undergo a Dakin-West reaction,[116] gives an isobutyl carbonate mixed anhydride that readily acylates amino acid esters with no evidence of ester formation. On the other hand, acylamino acids which readily undergo the Dakin-West reaction will also form esters with an alkyl chloroformate in the presence of base. Ester formation is not usually a serious side reaction, when it is, a mixed anhydride may be selected that will avoid it.

An obvious similarity exists between the formation of an ester from an α-acylamino acid alkyl carbonate via a modified Dakin-West reaction and the formation of a peptide derivative from an acylamino acid and a carbonyl amino acid ester (isocyanate).[118]

$$R_1CONHCHR_2CO_2H + OCNCHR_3CO_2C_2H_5 \rightarrow$$
$$R_1CONHCHR_2COOCONHCHR_3CO_2C_2H_5$$
$$XXIII$$

$$XXIII \xrightarrow[60°]{Pyridine} R_1CONHCHR_2CONHCHR_3CO_2C_2H_5 + CO_2$$

[124] King and McMillan, *J Am Chem Soc*, **72**, 4911 (1951).
[125] King and McMillan, *J Am Chem Soc*, **77**, 2814 (1955).
[116] Goldschmidt and Wick, *Z. Naturforsch*, **5B**, 170 (1950).

The decomposition of the intermediate XXIII is catalyzed by pyridine,[117] the catalyst used in the original Dakin-West experiments.[118]

Urethan Formation. Although early investigators failed to report any evidence of urethan formation in the reaction of a mixed carbonic anhydride with an amine, more extended observations have shown that urethans are sometimes formed. For example, the reaction of N-benzoyl-β-ethyl-α-DL-aspartyl ethyl carbonate (XXIV) with glycyl-n-hexylamide gave an 80% yield of the expected dipeptide derivative XXV but also gave the ethyl urethan of glycyl n-hexylamide (XXVI).[101]

This has been interpreted as due either to attack of the amine at the carbethoxy carbonyl (route b) or to the presence of unreacted ethyl chloroformate which had failed to form mixed anhydride.

The reaction of formylglycyl ethyl carbonate with ethyl p-aminobenzoate to give the ethyl urethan of ethyl p-aminobenzoate in 55% yield[13] has been mentioned previously (p. 164). Extensive urethan

[117] Goldschmidt and Krauss, *Angew. Chem.*, **67**, 471 (1955).
[118] Dakin and West, *J. Biol. Chem.*, **78**, 91, 745 (1928).

formation was noted both in the coupling of the isobutyl chloroformate mixed anhydride of 2-acetamidopelargonic acid with amines[113] and in the attempted coupling of the mixed anhydrides of pyruvic acid with esters of amino acids.[15] In the latter case, a cyclic intermediate may alter the point of attack of the amino acid ester from that which would normally be expected. Amides of pyruvic acid may be prepared from the acid and amines using phosphorus oxychloride[119] or dicyclohexylcarbodiimide.[120]

In the preparation of higher peptides such as a pentapeptide, the condensation of an α-acylamino acid mixed anhydride with a tetrapeptide would result in a high-molecular-weight urethan by-product difficult to separate from the product, whereas the condensation of an acylamino-tetrapeptide mixed anhydride with an amino acid ester would result in a low-molecular-weight urethan which would be much easier to remove.[61]

Reactions with the Solvent. Dimethylformamide reacts exothermically with ethyl or isobutyl chloroformate to give an essentially quantitative yield of carbon dioxide.[15] Dimethylformamide has such unusual solvent properties that it is the favorite solvent for the preparation of mixed carbonic anhydrides of more complex products such as sodium or potassium benzylpenicillinate[121] (although methylene chloride is preferred when triethylammonium benzylpenicillinate is used), sodium pantothenate,[73, 75, 122] and the amino-nucleoside derived from puromycin.[123] Carbobenzyloxypuromycin was prepared in 64% yield from the anhydride of carbobenzyloxy-*p*-methoxy-L-phenylalanine and ethyl chloroformate with the amino-nucleoside in dimethylformamide, but attempts to prepare analogs of puromycin with phthaloylglycine or carbobenzyloxyglycine in the same manner gave poor yields and variable results.

No change in yield of phthaloylglycylanilide was observed when dimethylformamide was used in place of chloroform as a solvent.[84] Phthaloylglycyl-*p*-aminobenzoic acid appears to form anhydrides with both ethyl and isobutyl chloroformates in dimethylformamide, but the *starting material* is recovered unchanged after attempted couplings with glutamic acid and glycine.[15] However, the anhydride of carbobenzyloxy-L-leucyl-L-alanyl-L-valyl-L-phenylalanylglycine and isobutyl chloroformate reacted with benzyl L-prolinate in dimethylformamide to give a 60% yield of carbobenzyloxyhexapeptide ester.[124] Pantothenate also was prepared in 50% yield from the mixed anhydride obtained by treating

[113] Wieland and Henke, *Angew Chem*, **69**, 362 (1957).
[114] Stoll, Hofmann, Leemann, Ott, and Schenk, *Helv Chim Acta*, **39**, 1165 (1956).
[115] Johnson, *J Am Chem Soc*, **75**, 3636 (1953).
[119] Baddiley and Mathias, *J Chem Soc*, **1954**, 2803.
[120] Baker, Joseph, and Williams, *J. Am. Chem Soc*, **77**, 1 (1955).
[121] Vaughan and Eichler, *J. Am. Chem Soc*, **76**, 2474 (1954).

a suspension of sodium pantothenate in dimethylformamide with ethyl chloroformate.[75]

Reactions in dimethylformamide involve the competition between anhydride formation and decomposition of the alkyl chloroformate, and yields will probably depend upon the rate at which the acid reacts to form the anhydride. Difficulty in using dimethylformamide as a solvent would be anticipated only for those acids which react relatively slowly to form mixed anhydrides.

Reactions with Tertiary Bases. Chloroformates react with tertiary bases to give products which include carbon dioxide, quaternary salts, and the tertiary base hydrochloride.[125,126] This reaction is normally slow enough so that it causes no interference with the anhydride-forming step. However, ethyl chloroformate appears to react faster with triethylamine than with anions of hindered acids such as tritylvaline or tritylleucine. Although it was assumed that these tritylamino acids were converted to mixed anhydrides in benzene with ethyl chloroformate (because of the formation of triethylamine hydrochloride), the products failed to react with methylaniline or glycine ester even when heated for 1 hour on a water bath.[9] However, mixed anhydrides of tritylamino acids and dicyclohexylcarbodiimide react to form peptides in satisfactory yields.[11,103] Thus the formation of triethylamine hydrochloride should not be interpreted as proof that anhydride formation has occurred.

Azlactone Formation. Reaction of 2-phenylacetamidoacrylic acid (XXVII) with ethyl chloroformate in chloroform at $-18°$ followed by the addition of aniline gave a 9% yield of the anilide XXVIII; the pseudo-azlactone XXIX was the major product.[127] Since the pseudo-

azlactone XXIX does not react with aniline, it was concluded that both the anilide XXVIII and the pseudo-azlactone XXIX were derived from the mixed carboxylic carbonic anhydride, but that cyclization of the
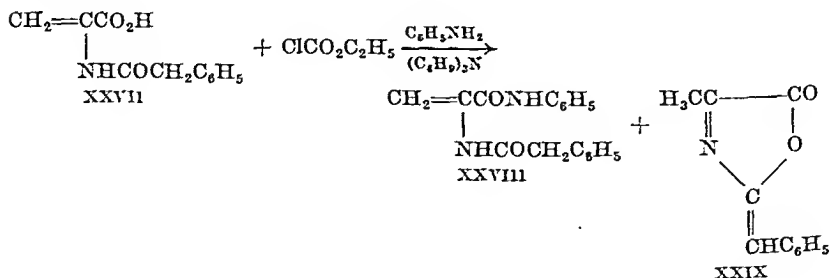
[125] H. T. Nagasawa, *Dissertation Abstr.*, **16**, 1803 (1956): Dissertation, Univ. of Minnesota.
[126] Gerrard and Schild, *Chem. & Ind. (London)*, **1954**, 1232.
[127] Brenner and Rufenacht, *Helv. Chim. Acta*, **37**, 203 (1954).

mixed anhydride to the pseudo-azlactone was very rapid. Other α,β-unsaturated α-acylamino acids XXX readily gave azlactones XXXI. It

$R_1 = CH_3$ or $C_6H_5 - R_2 = CH_3$ or $R_2 = C_6H_5$, $R_1 = H$
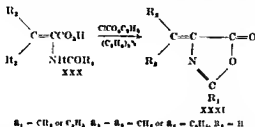
has been suggested that amide bond formation via mixed carboxylic carbonic anhydrides may proceed partly via azlactones.[187]

When a solution of hippuric acid in acetone at $-10°$ was treated with triethylamine and isobutyl chloroformate and an aqueous solution of ethyl glycinate added 20 minutes later, 25% of the hippuric acid was isolated as 2-phenyl-4-isopropylidene-5-oxazolone. It was also found, as expected on the basis of Bergmann's work,[138] that chloroacetyl-DL-phenylalanine was readily converted by isobutyl chloroformate to 2-methyl-4-benzyl-5-oxazolone.[89] Thus by-products may be anticipated when chloroacetylamino acids are used to prepare mixed anhydrides.

Diacylation. The mixed anhydride of carbobenzyloxyglycine and ethyl chloroformate reacts with diethyl L-glutamate to give a 36–41% yield of diethyl carbobenzyloxyglycyl-L-glutamate and a 17% yield of a by-product formulated as XXXII (R = $CH_2CO_2C_2H_5$), although the

$$Cbzo$$
$$CbzoNHCH_2CONCH_2CONHCHCO_2C_2H_5$$
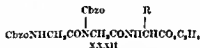
possibility that both carbobenzyloxyglycyl groups are on the nitrogen atom of diethyl glutamate has not been entirely excluded.[139] However, the same mixed anhydride reacts with ethyl glycinate to give a 30% yield of XXXII (R = H)[120a] With excess ethyl glycinate this by-product is not obtained. Steric effects may lessen this side reaction with other amino acids. Peptide synthesis with phosphorus oxychloride has led to similar by-products.[129]

Racemization. The general section on racemization at the beginning of this chapter should be consulted

[126] Bergmann, Zervas, and Lebrecht, *Ber.*, **54**, 2315 (1931)
[137] Schellenberg and Ullrich, *Chem. Ber.*, **92**, 1276 (1959)
[138] Kopple and Reneck, *J. Org. Chem.*, **23**, 1565 (1958)
[139] Wieland and Henke, *Ann.*, **599**, 70 (1956)

Racemization occurs with the mixed carboxylic carbonic anhydride procedure.[40, 131] A sample of optically pure α-benzoyl-L-lysyl-L-lysyl-L-lysine was quantitatively hydrolyzed to α-benzoyl-L-lysine and L-lysyl-L-lysine by trypsin, whereas the same benzoyl tripeptide prepared by the isobutyl chloroformate procedure[132] was hydrolyzed to only a small extent. Partial racemization also was observed when the mixed anhydride prepared from formyl-L-phenylalanine and ethyl chloroformate was condensed with glycine anilide.[133]
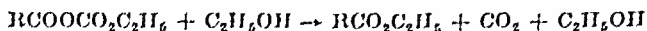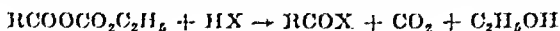
A comparison between the use of the ester of an amino acid and its hydrochloride with triethylamine has been reported.[40] Ethyl glycinate gave a higher over-all yield of dipeptide (65%) but also more of the DL-peptide (30% of the total yield) than did ethyl glycinate hydrochloride and triethylamine (53% over-all, 17% of the product DL). These results are in conflict with those of workers who have used other mixed anhydrides and report that the presence of triethylamine hydrochloride leads to increased racemization.

Miscellaneous Uses of α-Acylamino Alkyl Carbonates

Synthesis of Symmetrical Anhydrides. The formation of symmetrical anhydrides from α-acylamino acid alkyl carbonates is ordinarily an undesirable side reaction that results in decreased yields in peptide syntheses. In most instances disproportionation of a mixed to a symmetrical anhydride has been inferred to explain carbon dioxide evolution and relatively poor yields of peptide.

Disproportionation is not the best method to prepare symmetrical anhydrides from acyl alkyl carbonates because ester formation is an important competitive reaction.[134] Heating ethyl benzoyl carbonate in ethyl chloroformate under refluxing conditions gave ethyl benzoate and benzoic anhydride in a 10:7 ratio.[125]

In view of the great reactivity of carbonic acid mixed anhydrides with compounds of the type HX (where HX is an acid, amine, alcohol, thiol, water, etc.) it is apparent that esters could be formed by a chain reaction.

$$RCOOCO_2C_2H_5 + HX \rightarrow RCOX + CO_2 + C_2H_5OH$$

$$RCOOCO_2C_2H_5 + C_2H_5OH \rightarrow RCO_2C_2H_5 + CO_2 + C_2H_5OH$$

If HX is a carboxylic acid, RCO_2H, and is added in stoichiometric amount the product, RCOX, will be a symmetrical anhydride. By this method and ·

[131] Erlanger, Sachs, and Brand, *J. Am. Chem. Soc.*, **76**, 1806 (1954).

[132] Levin, Berger, and Katchalski, *Biochem. J.*, **63**, 308 (1956).

[133] Sheehan and Yang, *J. Am. Chem. Soc.*, **80**, 1154 (1958).

[134] Herzog, *Ber.*, **42**, 2557 (1909).

[135] Einhorn, *Ber.*, **42**, 2773 (1909).

with dioxane as a solvent, phthaloylglycine anhydride was prepared in 93% yield and carbobenzyloxyglycine anhydride in 50% yield. The method was also applied to the preparation of symmetrical carbobenzyloxypeptide anhydrides including carbobenzyloxyglycylglycine anhydride, which may be recrystallized from ethanol without decomposition.[136]

The yield of carbobenzyloxyglycine anhydride was increased from 50% to 81% by conducting the reaction in water in the presence of one equivalent of sodium hydroxide. Addition of water to carbobenzyloxyglycine ethyl carbonate (XXXIII) gave a 25% yield of the anhydride XXXIV. This suggests that carbobenzyloxyglycine formed by hydrolysis

$$C_6H_5CH_2OCONHCH_2COOC_2H_5 + C_6H_5CH_2OCONHCH_2CO_2Na \xrightarrow{H_2O}$$
$$\text{XXXIII}$$
$$(C_6H_5CH_2OCONHCH_2CO)_2O + C_2H_5OH + NaHCO_3$$
$$\text{XXXIV}$$
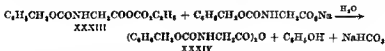
of the mixed anhydride reacts faster with the mixed anhydride than either anhydride reacts with water. Benzoyl ethyl carbonate reacts with water to give benzoic anhydride, carbon dioxide, and ethenol.[137]

Symmetrical anhydrides have been employed in peptide synthesis.[136] For example, carbobenzyloxyglycine anhydride (XXXIV) reacts with glycine in two equivalents of aqueous sodium hydroxide to give a 75% yield of carbobenzyloxyglycylglycine (XXXV). In the same manner

$$XXXIV + H_2NCH_2CO_2H \rightarrow$$
$$C_6H_5CH_2OCONHCH_2CONHCH_2CO_2H + C_6H_5CH_2OCONHCH_2CO_2H$$
$$\text{XXXV}$$

carbobenzyloxy diglycylglycine was prepared in 50% yield and phthaloylglycylglycine in 53% yield. However, phthaloyltriglycylglycine anhydride gave no isolable amounts of phthaloyltriglycylglycine on treatment with triglycine. Peptide syntheses by this procedure have the disadvantage of giving products from which by-products are difficult to remove.

Synthesis of Other Mixed Anhydrides. While reaction of an α-acylamino acid alkyl carbonate with an acid will lead to a new mixed anhydride, the reaction is not ordinarily useful in peptide synthesis since it adds an extra step, the original mixed anhydride is normally as useful as any mixed anhydride derived from it would be. However, thiol esters do possess certain advantages over acyl carbonic anhydrides for some purposes (see pp 241–255), and most of the literature on the preparation

Racemization occurs with the mixed carboxylic carbonic anhydride procedure.[40, 131]   A sample of optically pure α-benzoyl-L-lysyl-L-lysyl-L-lysine was quantitatively hydrolyzed to α-benzoyl-L-lysine and L-lysyl-L-lysine by trypsin, whereas the same benzoyl tripeptide prepared by the isobutyl chloroformate procedure[132] was hydrolyzed to only a small extent.   Partial racemization also was observed when the mixed anhydride prepared from formyl-L-phenylalanine and ethyl chloroformate was condensed with glycine anilide.[133]

A comparison between the use of the ester of an amino acid and its hydrochloride with triethylamine has been reported.[40]   Ethyl glycinate gave a higher over-all yield of dipeptide (65%) but also more of the DL-peptide (30% of the total yield) than did ethyl glycinate hydrochloride and triethylamine (53% over-all, 17% of the product DL).   These results are in conflict with those of workers who have used other mixed anhydrides and report that the presence of triethylamine hydrochloride leads to increased racemization.

Miscellaneous Uses of α-Acylamino Alkyl Carbonates

Synthesis of Symmetrical Anhydrides.   The formation of symmetrical anhydrides from α-acylamino acid alkyl carbonates is ordinarily an undesirable side reaction that results in decreased yields in peptide syntheses.   In most instances disproportionation of a mixed to a symmetrical anhydride has been inferred to explain carbon dioxide evolution and relatively poor yields of peptide.

Disproportionation is not the best method to prepare symmetrical anhydrides from acyl alkyl carbonates because ester formation is an important competitive reaction.[134]   Heating ethyl benzoyl carbonate in ethyl chloroformate under refluxing conditions gave ethyl benzoate and benzoic anhydride in a 10:7 ratio.[135]

In view of the great reactivity of carbonic acid mixed anhydrides with compounds of the type HX (where HX is an acid, amine, alcohol, thiol, water, etc.) it is apparent that esters could be formed by a chain reaction.

$$RCOOCO_2C_2H_5 + HX \rightarrow RCOX + CO_2 + C_2H_5OH$$

$$RCOOCO_2C_2H_5 + C_2H_5OH \rightarrow RCO_2C_2H_5 + CO_2 + C_2H_5OH$$

If HX is a carboxylic acid, RCO_2H, and is added in stoichiometric amount the product, RCOX, will be a symmetrical anhydride.   By this method and

[131] Erlanger, Sachs, and Brand, *J. Am. Chem. Soc.*, **76**, 1806 (1954).

[132] Levin, Berger, and Katchalski, *Biochem. J.*, **63**, 308 (1956).

[133] Sheehan and Yang, *J. Am. Chem. Soc.*, **80**, 1154 (1958).

[134] Herzog, *Ber.*, **42**, 2557 (1909).

[135] Einhorn, *Ber.*, **42**, 2773 (1909).

The concentration of the peptide necessary to have an equal chance for chain formation and for cyclization at the start of the reaction, assuming limited association, was calculated from the dimensions of the polypeptide chain. The use of a relatively polar solvent such as dimethylformamide to lessen the initial association of peptide molecules and the use of dilute solution were expected to favor cyclization. Initially it was found that triglycylglyceme and pentaglycylglycine were too insoluble to react with ethyl chloroformate. Since peptides containing different amino acids are generally more soluble than those containing a single amino acid, D-leucylglycylglycine was tried and found to be sufficiently soluble in dimethylformamide to react with ethyl chloroformate. Cyclization occurred upon the addition of tributylamine to give cyclo-(D-leucylglycylglycyl) in 37% yield.[140] The product gave no ninhydrin test and had no free amino or carboxyl group. Its solubility in butanol excluded the possibility of a long polymer chain. That the product might be a hexapeptide appeared to be statistically improbable.

More recent cyclization studies show that the character of the reaction product cannot be calculated on the assumption that chain length and dilution alone determine the reaction course. Polymerization of N-carboxyglycine anhydride[142] gave cyclo-(hexaglycyl) as the major product. Cyclization of triglycine azide, originally assumed to give cyclo-(triglycyl),[143] has been shown to give instead cyclo (hexaglycyl).[144, 145] Cyclization of the p-nitrophenyl esters of glycyl-L-leucylglycine and of glycyl-L-leucylglycylglycyl-L-leucylglycine gave the same crystalline cyclohexapeptide.[146] It has been shown that doubling is to be expected in cyclizing peptides with an odd number of amino acids.[145-149] An excellent summary of the problems of synthesizing cyclic peptides has appeared.[149a]

Experimental Conditions

Order of Addition of Reactants. In the preferred method of synthesis the α-acylamino acid is dissolved in an inert solvent in the presence of one equivalent of a tertiary base, the alkyl chloroformate added to form the mixed anhydride, and then the amine to be acylated is

141 Ballard, Bamford, and Weymouth, Proc. Roy. Soc. (London), 227A, 155 (1955).

142 Sheehan and Richardson, J. Am. Chem. Soc., 76, 6329 (1954).

143 Bamford and Weymouth, J. Am. Chem. Soc., 77, 6368 (1955).

144 Sheehan, Goodman, and Richardson, J. Am. Chem. Soc., 77, 6391 (1955).

145 Schwyzer and Gorup, Helv. Chim. Acta, 41, 2199 (1958).

146 Schwyzer, Sieber, and Gorup, Chimia (Switz.), 12, 90 (1958).

147 Schwyzer and Sieber, Helv. Chim. Acta, 41, 2186 (1958).

148 Schwyzer and Sieber, Helv. Chim. Acta, 41, 2190 (1958).

149 Schwyzer and Sieber, Helv. Chim. Acta, 41, 2194 (1958).

149a Amino Acids and Peptides with Antimetabolic Activity Ciba Foundation Symposium, Little Brown, and Co. Boston, 1958. See p 171

of new mixed anhydrides from acylamino acid alkyl carbonates pertains to the preparation of α-acylamino thiol esters.

The preparation of α-ketonitriles from acylamino acids via the mixed carbonic anhydride has not been reported, although it has been reported that α-ketonitriles will acylate amines.[138,139] Acylaminoacylcyanides would probably be unstable because of their tendency to polymerize.

Synthesis of Esters. It is occasionally desirable to esterify an amino acid. The synthesis of O-serine derivatives of α-acylamino acids has already been mentioned.

One practical point in acylating hydroxyl groups with carbonic acid mixed anhydrides was noted in the synthesis of esters of benzylpenicillin.[121] As ordinarily carried out, an alcohol is one product of the acylation reaction with an acyl alkyl carbonate. To avoid the presence of two different alcohols in the reaction mixture one may add an additional equivalent of triethylamine.

Benzylpenicillin ethyl carbonate

$$+ \text{ROH} + (C_2H_5)_3N \rightarrow$$

$$+ [OCO_2C_2H_5]^{\ominus}[(C_2H_5)_3NH]^{\oplus}$$
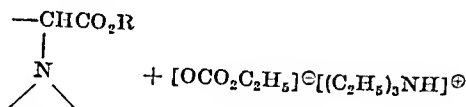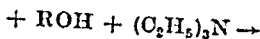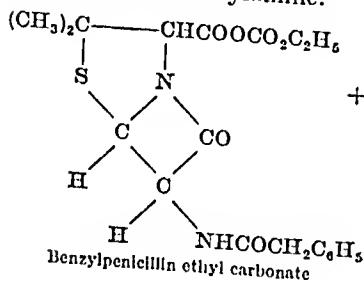
Cyclic Peptides. In model experiments the addition of ethyl chloroformate to an equivalent mixture of phthaloylglycine and ethyl glycinate gave the desired mixed anhydride and ethyl glycinate hydrochloride;[140] salt formation between phthaloylglycine and glycine ester effectively prevented appreciable urethan formation. Subsequent addition of tributylamine to the reaction mixture resulted in peptide bond formation.

The preparation of cyclic peptides presents three additional factors which are not important in linear polypeptide synthesis. They are the tendency to form linear polymers rather than cyclic products, the inability of the starting polypeptide in any suitable solvent, and the ability of the amide bond to exist in either *cis* or *trans* conformation.[141]

[138] Dornow and Theidel, *Angew. Chem.*, **66**, 605 (1954).
[139] Thesing and Witzel, *Ber.*, **88**, 117 (1955).
[140] Boissonnas and Schumann, *Helv. Chim. Acta*, **35**, 2229 (1952).
[141] Kenner, *J. Chem. Soc.*, **1956**, 3689.

obtained therefrom was not appreciably different from that obtained when a molar quantity of *sec*-butyl chloroformate was used in formation of the anhydride.[21]

Treatment of triethylammonium phthaloylglycinate with phenyl chlorothiolformate in cold chloroform leads to a rapid precipitation of phthaloylglycine anhydride, presumably via the pathway indicated.[155]
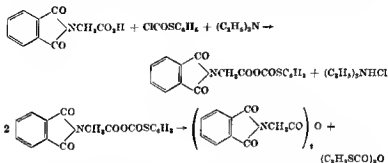
The use of *n*-hexyl chlorothiolformate in place of alkylchloroformates gave mixed anhydrides far less satisfactory for peptide bond formation.[18] The existence of phenyl thiolcarbonate XXXVI has been postulated as an intermediate in the reaction of phenylalanine with phenyl chlorothiolformate.[156]

XXXVI
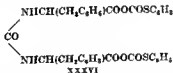
Tertiary Amines. Various tertiary amines may be employed to form the ammonium salts of the acylamino acid. Methyl- and ethyl-piperidine are commonly used by European chemists, whereas triethylamine is preferred in the United States. The use of tri-*n*-butylamine was suggested because its salts are soluble in most organic solvents[34] This very property, however, has led many investigators to use triethylamine. When the final reaction mixture is worked up, washing with dilute hydrochloric acid fails to remove the tri-*n*-butylamine from the organic layer. Concentration then gives a mixture (usually a solution) of product and tributylamine. Triisoamylamine proved to be even more difficult

[155] Bruckner and Kovács, *Acta Chim Acad Sci Hung*, **12**, 363 (1957)
[156] Crosby and Niemann, *J Am Chem Soc*, **76**, 4458 (1954)

introduced. Changing the order of addition results in decreased yields. For example, the tri-*n*-butylammonium salt of phthaloylglycine when allowed to react with ethyl chloroformate and then with ethyl glycinate gave a 70% yield of ethyl phthaloylglyeylglycinate. Reaction of the acid and glycine ester with ethyl chloroformate to give the mixed anhydride and ethyl glycinate hydrochloride followed by addition of tri-*n*-butylamine lowered the yield to 58%. Addition of ethyl chloroformate to a mixture of the other reactants gave a 27% yield.[140]

Alkyl Chloroformates. In non-aqueous solvents, branched-chain alkyl chloroformates would be expected to increase the electron density on the adjacent carbonyl group of the mixed anhydride and thus diminish the tendency toward urethan formation. The reaction of a series of carbobenzyloxy peptide alkyl carbonates with sodium glycinate in aqueous solution was investigated. The alkyl groups were methyl, ethyl, isopropyl, isobutyl, isoamyl, *n*-heptyl, *n*-octyl, benzyl, and phenyl; the acylated amino acids and peptides, carbobenzyloxyglycine, carbobenzyloxyglyeylglycine, and carbobenzyloxydiglycylglycine.[48] The ethyl and isopropyl carbonates gave the highest yields of acylated dipeptide whereas the higher alkyl esters gave better results with the higher peptides. A poor yield of impure carbobenzyloxyglycylglycine was obtained with the methyl ester, and the phenyl ester failed. The anhydrides of phthaloylglycine with either methyl or ethyl chloroformate gave the same yield of phthaloylglycylanilide.[54] *sec*-Butyl and isobutyl carbonates were the most satisfactory.[21, 56, 150–153] The anhydride of dicarbobenzyloxy-L-2,4-diaminobutyric acid with carbobenzyloxy chloride was used to make peptides.[154]

In addition to giving improved yields of peptides, mixed anhydrides formed from isobutyl chloroformate possess another practical advantage over those from ethyl chloroformate.[41] Neutral peptide intermediates are usually isolated by introduction of petroleum ether to an ethyl acetate solution. Any urethans formed as by-products will appear in the neutral fraction. The isobutyl urethans are more soluble in ethyl acetate-petroleum ether than are the ethyl urethans; thus purification of the product is easier.

A 50% excess of *sec*-butyl chloroformate in the formation of the anhydride with carbobenzyloxyglycine gave an impure product when coupled with ethyl-DL-phenylalaninate, but the amount of pure product

[150] Vaughan, U.S. pat. 2,713,574 (to American Cyanamide) [*C.A.*, **50**, 15580 (1956)].

[151] Vaughan, Can. pat. 536,345 (to American Cyanamide).

[152] King, Clark-Lewis, Wade, and Swindin, *J. Chem. Soc.*, **1957**, 873.

[153] Schumann and Boissonnas, *Helv. Chim. Acta*, **35**, 2237 (1952).

[154] Zaoral, Rudinger, and Sorm, *Collection Czechoslov. Chem. Communs.*, **18**, 530 (1953); *Chem. Listy*, **47**, 427 (1953) [*C.A.*, **49**, 179a (1955)].

Isolation of the product is simplified when toluene and other water-immiscible solvents are used in place of dioxane, acetone, and like solvents. The reaction mixture may be washed directly with hydrochloric acid and sodium bicarbonate solution (in the case of neutral products) to remove by-products without the necessity of replacing the original solvent.

The amount of solvent appears to be unimportant.[21]

Time, Temperature, and Stability. Temperature is reported to be the most critical factor in the preparation of mixed carbonic anhydrides; the anhydrides are too unstable to permit the use of temperatures above 15° and the reaction rate becomes too slow at temperatures below −20°.[21] Although a number of peptide derivatives have been prepared at 10° in dioxane,[34] the importance of keeping the reaction temperature at 0° to minimize disproportionation must be stressed.[46] A temperature of −5° permits the preparation of the mixed anhydride in good yield in 5 to 10 minutes in most cases. Carbobenzyloxyglycine forms a mixed carbonic anhydride within 30 seconds at −5°, but more complex amino acids require a longer reaction period. Although no decrease in yield in the preparation of phthaloylglycylanilide was observed whether the aniline was added to the anhydride at 0° after 10, 30, or 60 minutes,[54] there appears to be no advantage in prolonging the anhydride-forming step beyond 20 minutes.

The carbobenzyloxy group was removed from the α,α-dimethyl ester of carbobenzyloxy-γ-L-glutamyl-L-glutamyl ethyl carbonate,[141-143] as well as from its isomer involving mixed anhydride formation on the alpha carboxyl group,[144] by hydrogenolysis in cold dioxane or dimethylformamide with a palladium catalyst. The resulting mixed anhydrides were used for the preparation of polymers.

Mixed anhydrides formed between many types of organic acids and ethyl chloroformate in the presence of a tertiary base have been known for more than fifty years.[37] Their existence in solution was postulated as early as 1888.[127] Recently it has been found that many of these anhydrides are relatively stable compounds that may be distilled,[165,166] one, p-nitrobenzoyl anisyl carbonate, has been recrystallized[167] Various mixed anhydrides of benzylpenicillin have been obtained as gums in analytically pure form.[168] Phthaloylglycylglycyl ethyl carbonate has been obtained crystalline.[128]

141 Bruckner, Kováes, Nagy, and Kajtár, Naturwiss., 41, 528 (1958)
142 Bruckner, Kováes, Nagy, and Kajtár, Acta Chim Acad Sci Hung, 6, 219 (1955)
143 Bruckner, Wein, Nagy, Kajtár, and Kováes, Naturwiss., 42, 219 (1955)
144 Bruckner, Szekerke, and Kováes, Naturwiss., 42, 179 (1955)
145 Tarbell and Leister, J Org Chem., 23, 1149 (1958)
146 Windholz, J Org Chem., 23, 2044 (1958)
147 Leffler, J Am Chem Soc., 72, 87 (1950)
148 Johnson and Sheehan, U S pat 2,751,379 (to Bristol Laboratories) [C A., 51, 4438h (1957)].

to remove. In the preparation of ethyl carbobenzyloxy-DL-phenyl-alanyl glycinate, removal of the solvent after washing with acid and base gave two layers. The product was isolated by decanting the upper layer of triisoamylamine and triturating the bottom layer with ether.[157]

Although a moderate excess of triethylamine[21] or tri-*n*-butylamine[51] has been reported to have no effect on yields, a large excess may be undesirable. Chloroformates react with tertiary amines,[126] and it is possible that mixed anhydrides will also be decomposed by an excess of triethylamine or other relatively strong bases.[125]

Dimethylaniline has been recommended as a substitute for triethylamine since it does not react with chloroformates at room temperature.[125]

The use of metallic salts of the acylamino component rather than the acid and an organic base has received little attention except for the preparation of penicillin derivatives, where dry metallic salts are commercially available. Metallic salts of acylamino acids are unavailable, are troublesome to prepare, and are less soluble in the available solvents than are amine salts.

Solvents. A wide variety of solvents has been used for the preparation of mixed anhydrides, the more usual being dry chloroform, toluene, tetrahydrofuran, and dimethylformamide. The reaction fails in water,[140] and the use of moist chloroform or toluene results in a 10–15% decrease in yield.[21] However, mixed anhydrides of penicillin have been made in aqueous acetone,[158, 159] and, when dimethylaniline is used in place of the more usual triethylamine, reactions in aqueous solvents are possible.[125] Aqueous nitromethane proved to be better than water alone; as all the experiments were performed with glycine derivatives which form anhydrides relatively rapidly, it is not known whether this practice can be extended to other amino acids. Many reactions have been run in dioxane at 10°,[54] but the relatively high temperature dictated by the freezing point of dioxane sometimes resulted in disproportionation of the mixed anhydride. Better results were obtained in acetone at −10°.[65] The anhydride of α-tosyl-ε-carbobenzyloxy-L-lysine and ethyl chloroformate reacted with benzyl *p*-aminobenzoate to give a 21% yield of product in tetrahydrofuran, a 14% yield in dioxane, and an 11% yield in chloroform.[160] However, there is no reason to expect parallel changes in yield with other reactants in these solvents.

Racemization is greater in chloroform[40] and dimethylformamide[41] than in dioxane, toluene, tetrahydrofuran, or toluene-dioxane mixtures.

[157] Schlögl, Wessely, and Wawersich, *Monatsh.*, **85**, 957 (1954).
[158] Jansen and Hamlet, Brit. pat. 727,481 (to Glaxo Laboratories) [*C.A.*, **50**, 5036d (1956)].
[159] Belg. pat. 518,063 (to Glaxo Laboratories) (1953).
[160] Barrass and Elmore, *J. Chem. Soc.*, **1957**, 3134.

When the reaction solvent is miscible with water, the solvents may be removed by concentration in vacuum and the residue taken up in a mixture of ethyl acetate and water. Chloroform is sometimes superior to ethyl acetate for dissolving the product

When the product is a peptide acid, it will appear as the sodium salt in the aqueous sodium bicarbonate, which may be extracted with ethyl ether and acidified with hydrochloric acid to precipitate the product.

If the reaction did not proceed in nearly quantitative yield, the α-acylamino acid starting material will precipitate with the product. Sometimes purification by recrystallization is satisfactory; in other cases it is not at all practical This must be determined experimentally. If a carbobenzyloxyglycyl-DL-amino acid proves to be easy to purify, it does not follow that the carbobenzyloxyglycyl-L-amino acid may also be readily purified. Countercurrent distribution or fractional extraction may be necessary. Aqueous ethanol as well as ethyl acetate-petroleum ether are commonly used to recrystallize acylamino peptides.

Experimental Procedures

Ethyl Carbobenzyloxy-S-benzyl-L-cysteinyl-S-benzyl-L-cystein-ate.[170] A solution of 346 g. of carbobenzyloxy-S-benzyl-L-cysteine and 139 ml. of triethylamine in 3 l. of toluene was chilled to −5° and treated with 131 ml. of isobutyl chloroformate. After 10 minutes a cold solution of 276 g. of S-benzyl-L-cysteine ethyl ester hydrochloride and 139 ml. of triethylamine in 2 l. of chloroform was added, and the mixture allowed to stand overnight at 25°. One additional liter of chloroform was added, and the mixture was washed successively with water, aqueous bicarbonate, and water, and finally dried over anhydrous sodium sulfate. The filtrate was concentrated in vacuum to a small volume, and triturated with petroleum ether. The precipitated carbobenzyloxy-S-benzyl-L-cysteinyl-S-benzyl-L-cysteine ethyl ester was collected and recrystallized from ethanol. The yield was 382 g. (67%) of product, m.p. 105° (cor.)

Carbobenzyloxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteine.[64] To a solution of 4.0 g. of carbobenzyloxy-L-glutamine in 60 ml. of tetra-hydrofuran and 60 ml. of dioxane at −5° were added 2.0 ml. of triethylamine and 1.35 ml. of ethyl chloroformate. A solution of asparaginyl-S-benzyl L-cysteine (prepared from 5.9 g. of the N-carbobenzyloxy derivative) in 20 ml. of water and sufficient 2N sodium hydroxide to bring the pH to 7.5 was then added to the solution of the anhydride. The reaction mixture was stirred for 3 hours, while being maintained at pH 7.5 by the addition of 4N sodium hydroxide as needed After the addition of

[170] Izumiya and Greenstein, *Arch Biochem Biophys*, **52**, 203 (1954).

Amide-Forming Step. After the anhydride has been prepared, the amine to be acylated is added to the anhydride, the cooling bath removed, and the reaction mixture stirred for about 4 hours at room temperature or allowed to stand overnight. Ethyl carbobenzyloxy-L-leucylglycinate was formed in 86% yield from carbobenzyloxy-L-leucyl *sec*-butyl carbonate in $\frac{1}{2}$ hour at room temperature.[169] The reaction time may be shortened to a few minutes by heating the reaction mixture rapidly to boiling and then cooling.[57]

The amine component may be dissolved in any suitable solvent. Amino acids and peptides are usually dissolved in normal aqueous sodium hydroxide; esters of amino acids or peptides may be dissolved in a solvent such as acetone, benzene, chloroform, dimethylformamide, dioxane, ether, ethyl acetate, or tetrahydrofuran. If the solvent used for the anhydride is immiscible with that used for the amine, vigorous stirring is necessary. Since carbon dioxide is formed during the acylation, care must be observed to avoid excessive foaming during the addition of the amine. With many organic solvents foaming is hardly noticed, but with toluene, or when an aqueous solution of the sodium salt of an amino acid is added to a mixed carbonic anhydride, brisk evolution of carbon dioxide results.

Isolation of Product. A variety of procedures has been used to isolate the peptide intermediate. If a solid is present in the reaction mixture it may be recovered by filtration and examined for water solubility. In most instances the solid will prove to be the hydrochloride of the tertiary amine used to neutralize the acylamino acid and will dissolve completely in water. In some cases part of the desired product is recovered directly from the reaction mixture and may be washed with water to remove amine salts.

If the reaction solvent is immiscible with water and the product is neutral, the reaction mixture may be washed (after filtration) with dilute hydrochloric acid to remove any unreacted amino acid ester, and then with salt water, and with aqueous sodium bicarbonate, to remove any remaining acylamino acid. In the synthesis of percarbobenzyloxy-L-arginine, triethylamine was used in place of aqueous sodium bicarbonate.[94] The use of salt water is usually advisable to avoid emulsions. The solution remaining after extraction is dried, filtered, and concentrated in vacuum. Neutral esters are best obtained crystalline by dissolving them in ethyl acetate and adding petroleum ether. Trituration with ether or nitromethane will sometimes bring about crystallization if ethyl acetate fails. If the product remains a syrup, it is normally pure enough to use for the next step, e.g., saponification, hydrogenation, deacylation.

[169] Zaoral and Rudinger, *Collection Czechoslov. Chem. Communs.*, **20**, 1183 (1955); *Chem. Listy*, **49**, 745 (1955) [*C.A.*, **50**, 4017 (1956)].

prepared in good yield by treatment of sodium penicillin in dimethylformamide at 5° with acetyl chloride [173] It underwent the normal anhydride reactions and reacted preferentially at the penicillin carbonyl group to give the corresponding amides By this method penicillin was coupled to amino acids. Besides acetyl chloride, other acid halides up to octadecanoyl were employed to form similar mixed anhydrides [174,175] Diphenylacetyl chloride and isobutyryl chloride appear to be preferable to other acid chlorides in this reaction.

The first application of a mixed anhydride of an α-acylamino acid and a carboxylic acid for peptide bond formation was reported in 1950 [172] The method stemmed from an attempt to synthesize azlactones [176] when it became apparent that a mixed anhydride could be an intermediate in azlactone formation In an effort to prepare and isolate such a mixed anhydride, the silver salt of carbobenzyloxyglycine was treated with acetyl chloride in ether A low-melting crystalline mixed anhydride resulted Recrystallization from benzene and petroleum ether resulted in disproportionation Treatment of the mixed anhydride with aniline and hydroxylamine gave carbobenzyloxyglycine anilide and hydroxamate, respectively. [177,178]

Mechanism

Mixed anhydrides of α-acylamino acids with carboxylic acids contain the grouping $R_1CONHCHR_2COOCOR_3$, and the comments previously made on p. 163 apply here. The mechanism of acylation reactions of mixed anhydrides has also been discussed by Tedder. [175] A number of mixed anhydrides have been allowed to react with hydroxylamine and the ratio of hydroxamic acids determined [179a] With hippuric acetic anhydride, hippurylation predominated over acetylation by a ratio of 3·1. With hippuric benzoic anhydride the ratio of hippurylation rose to 21·1 These results indicated liberation of the weaker acid The previously mentioned role of the solvent (see p. 163) in reversing or altering the normal course of the reaction should be kept in mind.

Anhydrides of carboxylic acids and trifluoroacetic acid react with primary amines to give mixtures of amides in which the trifluoroacetamide usually predominates. [180] However, when the carboxylic acid is an

[172] Cooper and Brinkley, J Am Chem Soc, 76, 3966 (1949)
[173] Cooper, U S pat 2,577,699 (to Bristol Laboratories) [C A, 46, 7127c (1952)]
[174] Cooper, U S pat 2,593,852 (to Bristol Laboratories) [C A, 46, 7293f (1952)]
[175] Wieland, Kern, and Sehring, Ann, 569, 117 (1950)
[176] Brit pat 693,525 (to Boehringer Sohn) [C A, 49, 1783b (1955)]
[177] Brit pat 693,524 (to Boehringer Sohn) [C A, 49, 1782g (1955)]
[178] Tedder, Chem Rev, 55, 787 (1955)
[179a] Wieland and Stimming, Ann, 579, 97 (1953)
[180] Bourne, Henry, Tatlow, and Tatlow, J Chem Soc, 1952, 4014 Bourne, Randles, Tatlow, and Tedder, Nature, 168, 942 (1951)

350 ml. of ether the precipitate was collected, air-dried, dissolved in 70 ml. of water, and the solution brought to pH 2 with hydrochloric acid. The precipitate was again collected, air-dried, stirred for 1 hour at 20° with ethyl acetate, and finally collected to give 4.8 g. (64%) of carbo-benzyloxy-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteine, m.p. 90°.

Benzyl Carbobenzyloxy-L-leucyl-L-alanyl-L-valyl-L-phenylalanyl-glycyl-L-prolinate.[124] A solution of 1.30 g. (2 mmoles) of carbo-benzyloxy-L-leucyl-L-alanyl-L-valyl-L-phenylalanylglycine and 0.40 g. (4 mmoles) of triethylamine in 25 ml. of dimethylformamide was cooled to −5° and 0.31 g. (10% excess) of isobutyl chloroformate was added with stirring. After 10 minutes at this temperature, a solution of 0.48 g. (2 mmoles) of benzyl L-prolinate hydrochloride in 20 ml. of dimethyl-formamide was added and the mixture heated rapidly to about 70°, then immediately cooled. On addition of an excess of water, the product precipitated as a colorless solid. Two recrystallizations of this material from 40-ml. portions of 50% acetic acid gave 1.00 g. (60%) of product as colorless, microcrystalline prisms, m.p. 210–212°, $[\alpha]_D^{22} + 53.5 \pm 0.3°$ ($c = 2.1\%$, glacial acetic acid).

α-ACYLAMINO ACID CARBOXYLIC ACID ANHYDRIDES

The reaction of the salt of an α-acylamino acid with an organic acid halide leads to the formation of an α-acylamino acid carboxylic acid anhydride as shown in the accompanying equation. The mixed anhydride may be used for peptide synthesis.

$$R_1CONHCHR_2CO_2H + ClCOR_3 + (C_2H_5)_3N \rightarrow$$
$$R_1CONHCHR_2COOCOR_3 + [(C_2H_5)_3NH]^+ + Cl^-$$
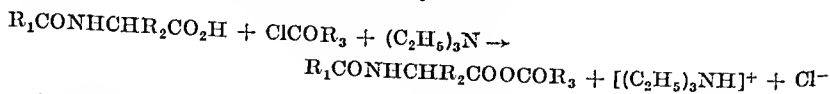
Curtius[171] used a mixed anhydride of this kind for a peptide bond synthesis as early as 1881. The reaction of benzoyl chloride with silver glycinate gave some benzoylglycylglycine. Curtius correctly assumed that the benzoylglycine initially formed would react further with benzoyl chloride to form a mixed anhydride; he was wrong in assuming that the mixed anhydride would be formed by displacement of benzoic acid to give hippuryl chloride rather than by displacement of the chlorine to give hippuryl benzoate. The correct course of the reaction was recently clarified.[172]

Although a method for the preparation of mixed carboxylic acid anhydrides was described in 1900,[79] this reaction was not used for peptide synthesis until recent years. In 1948 penicillin acetic anhydride was

[171] Curtius, *J. prakt. Chem.*, [2] 24, 239 (1881); 26, 145 (1882).
[172] Wieland and Sehring, *Ann.*, 569, 122 (1950).

dimethylformamide to give an acyclic mixed anhydride from which a 59% yield of tosyl-DL-alanine morpholide (XL) was obtained.[183] The reaction presumably proceeds as shown in the accompanying equations, although the structure of the intermediate anhydride was not determined.

Potassium tosyl-DL-alaninate gave a 45% yield of the morpholide starting with 3,5-dibromo-2-sulfobenzoic anhydride and an 8% yield with β-sulfopropionic anhydride

$$TosNHCH(CH_3)CO_2K + \begin{array}{c} CO \\ \diagdown \\ O \\ \diagup \\ SO_2 \end{array} \rightarrow TosNHCH(CH_3)COOC_6H_4SO_3K\text{-}o$$
XXXVII   XXXVIII   XXXIX

$$XXXIX + Morpholine \rightarrow TosNHCH(CH_3)CON\diagup O + HO_3C_6H_4SO_3K\text{-}o$$
XL
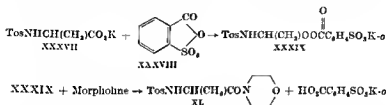
In a model experiment, dry potassium phenylacetate dissolved immediately in dimethylformamide upon addition of o-sulfobenzoic anhydride, but introduction of excess aniline gave only a 50% yield of anilide. The authors concluded that either the mixed anhydride disproportionated or, more probably, the amine attacked at both carbonyl positions.[183] An alternative explanation is that the intermediate mixed anhydride XLI undergoes a Perkin reaction to give the ketone XLII.

$$C_6H_5CH_2CO_2K + \begin{array}{c} CO \\ \diagdown \\ O \\ \diagup \\ SO_2 \end{array} \rightarrow C_6H_5CH_2COOC_6H_4SO_3K\text{-}o$$
XLI

$$XLI \rightarrow C_6H_5CH_2COC_6H_4SO_3K\text{-}o + CO_2$$
XLII
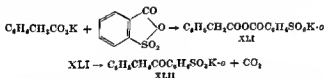
The mixed cyclic anhydrides of sulfocarboxylic acids have not been used with acylamino acids to form peptides, although the synthesis of tosylalanine morpholide indicates that it should be possible to do so.

An investigation of the use of the trifluoroacetyl group as an amine blocking group,[184,185] showed that the addition of 1 mole of amino acid to 1 mole of trifluoroacetic anhydride gave crystalline trifluoroacetylamino acids but that excess anhydride gave other products. DL-Alanine and DL-valine gave liquids (boiling at 36° and 45°, respectively, at 0.02 mm) that were formulated as mixed anhydrides although in each case the carbon, hydrogen, and nitrogen values fell between those calculated for the mixed anhydride and those calculated for the oxazolone or for the

[183] Kenner and Stedman, J. Chem. Soc. 1952, 2089.
[184] Weygand and Csendes, Angew. Chem., 64, 136 (1952).
[185] Weygand and Geiger, Chem. Ber., 89, 647 (1956).

α-amino acid, the trifluoroacetamido acid amide is the main or exclusive product.[181] Furthermore, trifluoroacetyl-L-alanine is racemized in the formation of the trifluoroacetic acid mixed anhydride. These results suggest that the reaction proceeds by way of an azlactone.

$$H_2NCH(CH_3)CO_2H + 2(CF_3CO)_2O \rightarrow CH_3CHCOOCOCF_3 + 2CF_3CO_2H$$

$$\overset{|}{NHCOCF_3}$$

$$CH_3CH\!-\!\!-\!\!CO$$
$$\underset{N}{|}\qquad\underset{O}{|} \quad + CF_3CO_2H$$
$$\diagdown C \diagup$$
$$CF_3$$
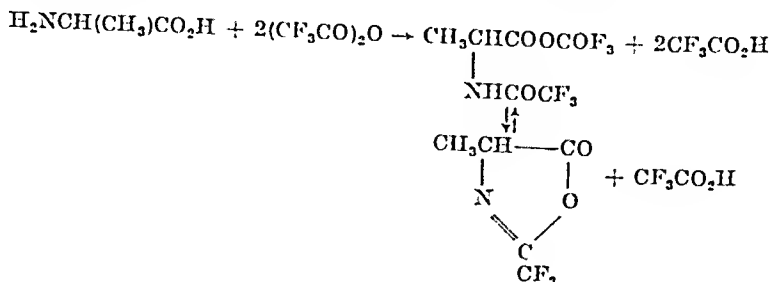
Trifluoroacetyl-L-proline trifluoroacetic anhydride disproportionates to trifluoroacetyl-L-proline anhydride, which has been used to acylate ethyl glycinate in 47% yield.[182]

Scope and Limitations

Carboxylic Acids Used in Anhydride Formation. Initial work with acetyl chloride and benzoyl chloride[172, 176] showed that the benzoic acid mixed anhydride gave less disproportionation than the acetic acid mixed anhydride. In a systematic study mixed anhydrides of carbobenzyloxyglycine and a number of carboxylic acids were prepared and allowed to react with aniline, the yields and melting points of the products being noted. Since anhydrous media were used, the results could be correlated with the prediction of Emery and Gold[3, 4] that, in anhydrous solvents, attack by the amine should occur at the carbonyl carbon atom having the lower electron density. The results confirmed the superiority of the mixed anhydride of benzoic acid over that of acetic acid. However, the α and β branched-chain acids were found to be better than any of the aromatic acids. In these branched-chain acids both the inductive and the steric effects of the alkyl groups operate to increase the attack by the amine at the amino acid carbonyl group. The aromatic acids, having relatively unfavorable electronic and inductive effects, generally gave lower yields of less pure product.[8]

The reactions of some cyclic mixed anhydrides of carboxylic and sulfonic acids with acylamino acids have been studied. Potassium tosyl-DL-alaninate (XXXVII) reacts with o-sulfobenzoic anhydride (XXXVIII) in

[181] Weygand and Leising, *Chem. Ber.*, **87**, 248 (1954).
[182] Weygand, Klinke, and Eigen, *Chem. Ber.*, **90**, 1896 (1957).

of acylamino acids with benzoic, isovaleric, and trifluoroacetic acids. Ethyl carbobenzyloxyglycyl-DL-phenylalaninate has been prepared using the mixed anhydrides of carbobenzyloxyglycyl-DL-phenylalanine and trimethylacetic and diethylacetic acids.²

α-Acylamino Acids Used in Anhydride Formation. Anhydrides prepared from isovaleryl chloride and acyl derivatives of glycine, alanine, leucine, norleucine, proline, phenylalanine, asparagine, and lysine have been employed for the synthesis of peptides. The use of anhydrides derived from isovaleryl chloride and sarcosine, D-isoleucine and D-isoleucyl-L-proline have been reported but with no details.¹⁸⁸ Dehydration of the amido group of asparagine to the nitrile, observed when the pyrophosphate or carbodiimide method is used, does not occur when the anhydride derived from isovaleryl chloride and carbobenzoyl-L-asparagine is coupled with S-benzyl-L-cysteine.⁹⁷ Low yields (10–30%) were obtained in the acylation of allothreonine with the anhydrides prepared from the carbobenzyloxy derivatives of alanine, norleucine, and phenylalanine.¹⁸⁹

The anhydride derived from benzoyl chloride was used to prepare an extensive series of lysine peptide intermediates.¹⁹⁰,¹⁹¹ This procedure was reported to be simpler experimentally and to give purer products than the azide method. These results represent the only reported experiments in which mixed anhydrides of optically active acylamino polypeptides and carboxylic acids have been used. Racemization was not a problem even though a lysine pentapeptide derivative was synthesized by the addition of one lysine ester group at a time to a percarbobenzyloxylysine polypeptide. Mixed anhydrides of benzoic acid and N-formyl-O-acetyl-L-tyrosine, N-carbobenzyloxy-O-acetyl-L-tyrosine, carbobenzyloxy- and phthaloyl-glycine, carbobenzyloxy-DL-alanine, carbobenzyloxyglycylglycylglycine, and carbobenzyloxy-DL-alanyl-DL-alanine have also been prepared.

The mixed anhydride of trifluoroacetylglycine and trifluoroacetic acid reacts with ethyl glycinate to give more than 60% of ethyl trifluoroacetylglycylglycinate. Reaction of ethyl glycinate with the anhydride of trifluoroacetyl-DL-alanine and trifluoroacetic acid gave ethyl trifluoroacetyl-DL-alanylglycinate in 55% yield. Glutamic acid reacts with trifluoroacetic anhydride to give the anhydride of N-trifluoroacetyl-L-glutamic acid.¹⁸¹

No information is available on the possible use of mixed anhydrides of the hydroxy amino acids such as serine and threonine. Pantotheine,

¹⁸⁸ Franck, *Angew. Chem.*, **69**, 237 (1957).
¹⁸⁹ Botvinik, Avers, and Noskova *Zhur. Obshchei Khim.*, **26**, 2325 (1956) [*C. A.*, **51**, 4945, (1952)].
¹⁹⁰ Waley and Watson, *J. Chem. Soc.*, **1953**, 475.
¹⁹¹ Waley and Watson, *Biochem. J.*, **57**, 529 (1954).

symmetrical trifluoroacetylamino acid anhydride. Later it was shown that heating trifluoroacetic anhydride with trifluoroacetyl-DL-alanine to 140° gave 2-trifluoromethyl-4-methyl-5-oxazolone contaminated with trifluoroacetic acid.[186] The symmetrical trifluoroacetyl-DL-alanine anhydride gave the oxazolone on heating.

The use of the mixed anhydrides of trifluoroacetic acid and an α-acylamino acid for peptide synthesis suffers a serious disadvantage in that racemization is observed even at relatively low temperatures. A second disadvantage is that excess trifluoroacetic anhydride acylates the peptide nitrogen atom. Subsequent treatment with the ester of an amino acid will result in the cleavage of some peptide bonds. For example, the anhydride prepared from glycyl-DL-alanine and an excess of trifluoroacetic anhydride reacts with ethyl glycinate to give a mixture of trifluoroacetylglycyl-DL-alanylglycine ester, trifluoroacetylglycylglycine ester, trifluoroacetyl-DL-alanylglycine ester, and trifluoroacetylglycine ester.[187]

$$H_2NCH_2CONHCH(CH_3)CO_2H + (CF_3CO)_2O \rightarrow$$

$$CF_3CONHCH_2CONCH(CH_3)COOCOCF_3$$

$$\underset{\substack{| \\ COCF_3 \\ \text{XLIII}}}{}$$

$$XLIII + H_2NCH_2CO_2C_2H_5 \rightarrow$$

$$\begin{cases} CF_3CONHCH_2CONHCH(CH_3)CONHCH_2CO_2C_2H_5 \\ CF_3CONHCH_2CONHCH_2CO_2C_2H_5 \\ CF_3CONHCH(CH_3)CONHCH_2CO_2C_2H_5 \\ CF_3CONHCH_2CO_2C_2H_5 \end{cases}$$
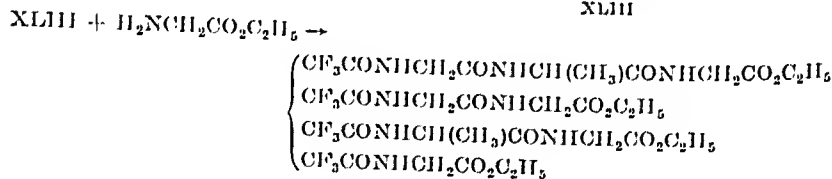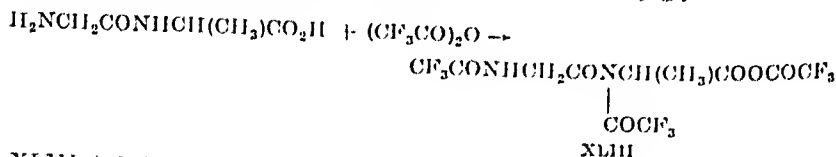
Heating phthaloylglycine with oxalyl chloride for 48 hours in benzene gave phthaloylglycine anhydride in 99% yield. The same reactants heated for 6 hours gave the mixed anhydride XLIV,[136] which was not used
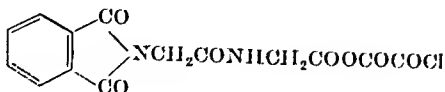
XLIV

for peptide synthesis, and would appear not to be suitable for this purpose since 2 moles of amino acid ester or peptide ester would be required per mole of mixed anhydride.

In spite of the considerable number of mixed anhydrides of α-acylamino acids and carboxylic acids that have been prepared, peptide bond formation has actually been attempted with only a few, namely the anhydrides

[186] Weygand and Glöckler, *Chem. Ber.*, 89, 653 (1956).
[187] Weygand, Geiger, and Glöckler, *Chem. Ber.*, 89, 1543 (1956).

contribute to lowered yields even when the substituted benzamides do not interfere with the purification of the desired products.[8] The mixed

$$R_1CONHCHR_2CONR_2R_4 +$$
$$C_6H_5CO_2H +$$

$$R_1CONHCHR_2COCOC_6H_5 + HNR_3R_4 \Big\langle$$

$$C_6H_5CONR_3R_4 +$$
$$R_1CONHCHR_2CO_2H$$
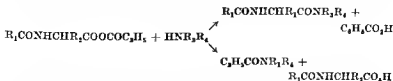
anhydrides of trifluoroacetylamino acids and acetic or benzoic acid react with aniline to give mixtures of anilides difficult to separate. Trifluoroacetyl-DL-alanyl acetate gave only a 6% yield of trifluoroacetyl-DL-alanylanilide[123]

Experimental Conditions

The preparation of an α-acylamino acid carboxylic acid mixed anhydride involves reaction of an α-acylamino acid salt with a carboxylic acid chloride or, for mixed anhydrides of trifluoroacetic acid, trifluoroacetic anhydride.

In earlier work the silver salt of the α-acylamino acid in ether or benzonitrile[176,177] was employed. The latter solvent is especially suitable. Silver chloride was removed by centrifugation. The sodium salts were found to react more slowly than the silver salts, but the sodium salt of benzylpenicillin reacts rapidly with acetyl chloride in dimethylacetamide.[172] N-Ethylpiperidine[175] or triethylamine[9] is convenient for the preparation of the salts of an acylamino acid. Pyridine is usually less satisfactory, and dimethylaniline is generally unsuitable because of its lower basicity.[175] Toluene, benzene, tetrahydrofuran and other inert solvents may be used.

The mixed anhydride is usually prepared between −5° and 5° in order to minimize disproportionation. For the same reason it is advisable to use the mixed anhydride without isolation.[172] The mixed anhydride may be prepared in a water immiscible solvent such as benzene and then treated, with vigorous stirring, with an aqueous solution of the sodium salt of the amino acid or peptide to be acylated. In this manner, carbobenzyloxy-DL-alanyl-DL-alanyl-DL-alanine (XLVII) was prepared in 80% yield[178]

$$C_6H_5CH_2OCONHCH(CH_3)CONH(CH_3)CO_2H + C_2H_5N(CH_3)_2 + C_4H_5COCl$$
$$\rightarrow C_6H_5CH_2OCONHCH(CH_3)CONH(CH_3)COOCOC_2H_5$$

XLVI + H_2NCH(CH_3)CONHCH_3CO_2H →

$$C_6H_5CH_2OCONHCH(CH_3)CONHCH(CH_3)CONHCH(CH_3)CO_2H$$
$$XLVII$$
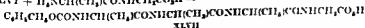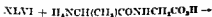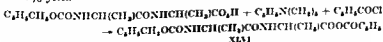
[177] Wieland and Sehring U.S. pat. 2,711,945 (to Boehringer Sohn) (C A 49, 12352 (1955)).

however, has been prepared in 38% yield from the mixed anhydride of benzoic acid and pantothenic acid which contains two hydroxyl groups.[75]

Acylglutamic acids in which the acyl group is acetyl, carbobenzyloxy, phthaloyl, 4-nitrobenzoyl, or phenacetyl react with acetic anhydride or thionyl chloride to form acylaminoglutaric anhydrides.[192] The same type of reaction would be likely to occur in an attempt to prepare mixed anhydrides of other carboxylic acids. When the acyl group of the amino acids is tosyl, the reaction takes a different course. Acetic anhydride or acetyl chloride leads to the formation of 1-tosylpyroglutamyl acetate (XLV).[193] Treatment of the anhydride XLV with ammonia leads to less
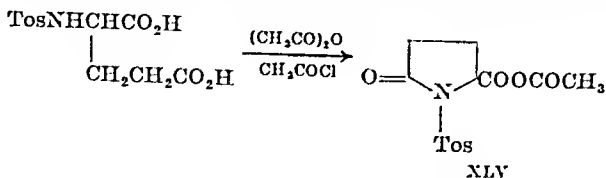
than a 50% yield of 1-tosylpyroglutamic acid amide, presumably because fission occurs at both carbonyl groups.[192]

1-Tosylpyroglutamyl chloride[107, 194, 195] will probably prove as useful as any mixed anhydride of 1-tosylpyroglutamic acid and a carboxylic acid.

Side Reactions

The principal side reaction observed in the use of mixed anhydrides of α-acylamino acids and carboxylic acids has been disproportionation.

$$2R_1CONHCHR_2COOCOR_3 \rightarrow (R_1CONHCHR_2CO)_2O + (R_3CO)_2O$$
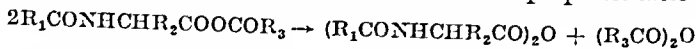
The mixed anhydrides with benzoic acid are less prone to this reaction than those with acetic acid, but upon warming they too disproportionate.[176] Carbobenzyloxy-DL-alanine benzoate when warmed just above its melting point for 10 minutes gave benzoic anhydride and carbobenzyloxy-DL-alanine anhydride in good yield. Silver carbobenzyloxyglycylglycinate and benzoyl chloride in benzonitrile gave a mixture of carbobenzyloxyglycylglycyl benzoate and carbobenzyloxyglycylglycine anhydride.[176]

Although mixed anhydrides of α-acylamino acids and benzoic acid can react at either carbonyl groups, no benzamide has been observed as a by-product in this type of peptide synthesis except when the amine-protecting group is trifluoroacetyl.[196] However, this side reaction may

[192] Rudinger, *Collection Czechoslov. Chem. Communs.*, 19, 365 (1954). Published in Czech. in *Chem. Listy*, 48, 235 (1954) [*C.A.*, 49, 3126b (1955)].
[193] Harrington and Moggridge, *J. Chem. Soc.*, 1940, 706.
[194] Stedman, *J. Am. Chem. Soc.*, 79, 4691 (1957).
[195] Swan and du Vigneaud, *J. Am. Chem. Soc.*, 76, 3110 (1954).
[196] Weygand and Reiher, *Chem. Ber.*, 88, 26 (1955).

mixture added to 7.1 g of ε-carbobenzyloxy L lysine methyl ester in 90 ml of ethyl acetate and 30 ml of 1 4N aqueous potassium bicarbonate. The reaction mixture was vigorously stirred at 0° for 45 minutes, the precipitate collected and recrystallized from methanol to give 9.1 g (58%) of product, m p. 164–165 5° When the reaction was conducted in benzonitrile, a less pure product was obtained

CARBODIIMIDES

Carbodiimides, ketenimines, isocyanates, and ketenes all possess a central carbon atom having twinned double bonds, and all add carboxylic acids by 1,2 addition to give intermediates from which amides may be obtained.

Mechanism

The addition of carboxylic acids to carbodiimides has been studied in detail, and the course of the reaction has been shown to involve addition of a proton to the carbodiimide (XLVIII) followed by attack of the acid anion The relevant literature has been reviewed [200–203]
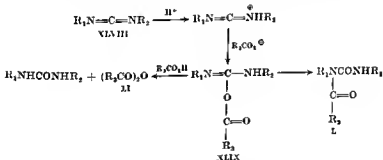
The intermediate adduct XLIX can either rearrange to an acylurea L or react with a second mole of acid to give a symmetrical anhydride LI and the urea. The adduct XLIX will be recognized as a nitrogen analog of an acyl alkyl carbonate mixed anhydride two oxygen atoms have been replaced by nitrogen The adduct is sensitive to base[202] and will react with an amino acid (or peptide) ester as shown in the accompanying

[200] Khorana, Chem Revs, 53, 145 (1953)
[201] Khorana, Chem & Ind (London), 1955, 1087
[202] Smith, Moffatt, and Khorana, J Am Chem Soc. 80, 6204 (1958).
[203] Khorana, J Chem Soc. 1952, 2081

The benzoic acid formed as a by-product may be removed by extraction with petroleum ether or by steam distillation.[172, 197]

The yields are generally higher if dry solvents are employed. The mixed anhydrides of carbobenzyloxyglycine and trimethylacetic acid, dimethylacetic acid, and isovaleric acid reacted with ethyl DL-phenylalaninate to give ethyl carbobenzyloxyglycyl-DL-phenylalaninate in 81, 84, and 86% yields, respectively, in anhydrous solvents but 58, 67, and 55% yields in wet solvents.

Although mixed anhydrides derived from benzoyl chloride have been used as frequently as those from isovaleryl chloride to synthesize peptides, the latter acyl halide in toluene with the triethylammonium salt of an acylamino acid appears to be preferable. About 1 or 2 hours are usually allowed for anhydride formation.[8, 198] However, when the mixed anhydride from dicarbobenzyloxy-L-lysine and benzoyl chloride was allowed to stand for only 2 minutes at 0° before adding L-tyrosinamide, the dipeptide amide was isolated in 70% yield.

Once the mixed anhydride has been prepared, the amide-forming step and the isolation of the product are essentially the same as for the acyl-amino alkyl carbonates already described (p. 194).

Experimental Procedures

Ethyl Carbobenzyloxy-L-prolyl-L-leucylglycinate (Use of Iso-valeryl Chloride).[199] A solution of 69.5 g. of carbobenzyloxy-L-proline and 28.2 g. of triethylamine in a mixture of 335 ml. of dry toluene and 335 ml. of dry chloroform was cooled to −5° and 33.8 g. of isovaleryl chloride added. After 1½ hours a cooled solution of ethyl N-leucyl-glycinate hydrochloride (from 100 g. of ethyl carbobenzyloxy-L-leucyl-glycinate) and 28.2 g. of triethylamine in 700 ml. of chloroform was added and the reaction mixture left overnight at 5°. The solution was then washed with water and 3% aqueous sodium bicarbonate, and concentrated under reduced pressure to a volume of approximately 500 ml. Dilution of the solution with hexane caused 120 g. of white crystalline product, m.p. 145–146°, to separate. One recrystallization from aqueous ethanol gave 115.5 g. (92%) of the carbobenzyloxytripeptide ester, m.p. 148–149° $[\alpha]_D^{22.5}$ −79.8° (c = 2.5%, ethanol).

Methyl Tetra-(N-carbobenzyloxy)-L-lysyl-L-lysyl-L-lysinate (Use of Benzoyl Chloride).[190] A solution of 11.1 g. of tricarbobenzyloxy-L-lysyl-L-lysine in 30 ml. of tetrahydrofuran containing 2.22 ml. of N-ethyl-piperidine was treated at 0° with 18.8 ml. of benzoyl chloride and the

[198] Vaughan, U.S. pat. 2,710,857 (to American Cyanamid) [C.A., 50, 5732g (1956)].
[199] Ressler and du Vigneaud, J. Am. Chem. Soc., 76, 3107 (1954).

carbobenzyloxyleucine and carbobenzyloxyphenylalanine in yields of 84% and 82%, respectively The optical configurations were presumably L.

Hydroxy Amino Acids. The successful use of carbobenzyloxy-L-serine[213-216] carbobenzyloxy-L-hydroxyproline[213, 217] and phthaloyl-L-threonine[213, 217] with the hydroxyl groups unprotected is noteworthy. Phthaloyl-L-threonyl-L-phenylalanine ethyl ester (96%), phthaloyl-L-threonyl-L-phenylalanyl-L-phenylalanine methyl ester (92%), and phthaloyl-L-threonyl-L-phenylalanylglycine ethyl ester (94%) were synthesized using N,N'-dicyclohexylcarbodiimide in methylene chloride at room temperature[213] Likewise, methyl L-isoleucinate was acylated by N-carbobenzyloxy-L-tyrosine in 94% yield,[218] and by N-formyl-L-tyrosine in 74% yield[42] Satisfactory results were obtained in the acylation of the methyl esters of L-tyrosine, L-tryptophan, and L-serine by carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosine.[219]

The reaction with hydroxyproline and allohydroxyproline very probably proceeds at least in part through the lactone, since N,N'-dicyclohexylcarbodiimide converts N-carbobenzyloxy-L-allohydroxyproline to its lactone, which reacts with glycine ester to give the dipeptide derivative.[220]

Acidic Amino Acids. The ability of N,N'-dicyclohexylcarbodiimide to promote the formation of amide bonds in aqueous media is illustrated by the synthesis of L-glutamine from L-glutamic acid.[221] The copper salt was used to protect the α-amino and adjacent carboxyl groups while the γ carboxyl group was converted to the amide This method should be applicable to the preparation of γ-glutamyl peptides.

Although N-trityl-L-asparagine reacted with methyl L-tyrosinate in the presence of N,N'-dicyclohexylcarbodiimide to give, after saponification of the intermediate, 50% of N-trityl-L-asparaginyl-L-tyrosine,[222] asparagine itself gave generally disappointing results, owing possibly to partial dehydration of the amide to the nitrile.[223] However, the readily accessible carbobenzyloxy-β-cyano-L-alanine does form a peptide bond with the aid of N,N'-dicyclohexylcarbodiimide.[223]

[213] Sheehan, Hess, and Goodman, 128 Meeting, Am Chem Soc, Minneapolis, Minn, Abstracts, p 26c.

[214] Hess, Sheehan, and Goodman, Federation Proc, 14, 226 (1955)

[215] Barr, Maurukas, and Clarke, J Biol Chem, 228, 181 (1957)

[216] Zahn and Diehl, Z Naturforsch, 12, 85 (1957)

[217] Sheehan, Goodman, and Hess, J Am Chem Soc, 78, 1367 (1956)

[218] Guttmann, Jaquenoud, and Boissonnas Naturwiss, 44, 632 (1957)

[219] Boissonnas and Guttmann, Helv Chim Acta, 43, 190, 200 (1960)

[220] Patchett and Witkop, J Am Chem Soc, 79, 185 (1957)

[221] Chang and Barker, U S pat 2,810,754 (to General Mills) (C 2, 63995 (1958))

[222] Chillemi, Scarso, and McCurtha, Gazz chim ital, 87, 537 (1957)

[223] Guh, Kutsoyannis, Hess, and Stedman, J Am Chem Soc, 78, 5934 (1956)

[224] Zaoral and Rudinger, Proc Chem Soc, (London), 1957, 176

equation. This reaction provides a versatile and convenient peptide synthesis.[201, 204, 204a]

$$XLIX + H_2NCH_2CO_2C_2H_5 \rightarrow R_1NHCONHR_2 + R_3CONHCH_2CO_2C_2H_5$$

Scope and Limitations

All the common amino acids have been used as the acylating species in peptide bond formation with N,N'-dicyclohexylcarbodiimide. The complete synthesis of oxytocin[205, 206] and a tyrosine homolog[207] using the carbodiimide method as the sole means of peptide bond formation has been described. The carbodiimide procedure was also employed extensively in synthesizing an ACTH-like peptide of twenty amino acids.[208] The synthesis of phenoxypenicillin was accomplished using N,N'-dicyclohexylcarbodiimide to close the β-lactam ring,[209] and the same carbodiimide served to prepare dimethylpyruvoyl-L-phenylalanine methyl ester in 86% yield.[120]

Trityl-γ-alkyl-L-glutamate,[103] ditrityl-L-histidine, trityl DL-methionine, and trityl-DL-tryptophan[11] may be used for formation of peptides. These reactions are of special interest because the same substituted amino acids in the form of their mixed anhydrides with carbonic acid failed to undergo coupling reactions. This effect was ascribed to steric hindrance;[10] either no anhydride is formed or the anhydride reacts to form the carbonate.[210] An alternative explanation is that the anhydride step becomes sufficiently slow that the reaction of the alkyl chloroformate with the triethylamine predominates. This complicating side reaction is impossible with the carbodiimides, and peptides are formed.

N,N'-Dicyclohexylcarbodiimide has been used to prepare polypeptides with average molecular weights as high as 1,000,000 from lower-molecular-weight polypeptides.[211]

N-Acetyl-DL-penicillamine is rapidly converted at room temperature to the β-thiolactone by N,N'-dicyclohexylcarbodiimide.[72]

O-Seryl derivatives have been prepared from N-benzoylserylglycine using N,N'-dicyclohexylcarbodiimide in pyridine. In a similar manner O-carbobenzyloxyaminoacyl-N-benzoylserylglycine[212] was prepared from

[204] Sheehan and Hess, *J. Am. Chem. Soc.*, 77, 1067 (1955).
[204a] Sheehan, U.S. pat. 2,938,892 (to Arthur D. Little) (1960).
[205] Velluz, Amiard, Bartos, Goffinet, and Heymès, *Bull. soc. chim. France*, 1956, 1464.
[206] Beyerman, Bontekoe, and Koch, *Rec. trav. chim.*, 78, 935 (1959).
[207] Beyerman, Bontekoe, and Koch, *Rec. trav. chim.*, 79, 105 (1960).
[208] Boissonnas, Guttmann, Waller, and Jaquenoud, *Experientia*, 12, 446 (1956).
[209] Sheehan and Henery-Logan, *J. Am. Chem. Soc.*, 79, 1262 (1957).
[210] Zervas and Theodoropoulos, *J. Am. Chem. Soc.*, 79, 1262 (1957).
[211] Blout and DesRoches, *J. Am. Chem. Soc.*, 81, 370 (1959).
[212] Shchukina, Kara-Murza, and Vdoviha, *Zhur. Obshchei Khim.*, 29, 340 (1959) [*C.A.*, 53, 21694c (1959)].

Unlike most other mixed anhydride reactions, the preparation of the anhydride and the formation of the peptide bond are not done separately. Instead, the α-acylamino acid (or peptide) and the amino acid (or peptide) ester are treated with a slight excess of N,N'-dicyclohexylcarbodiimide in a solvent such as acetonitrile. An exothermic reaction occurs. After 4 hours at room temperature, excess carbodiimide is destroyed by the addition of a small amount of acetic acid, the N,N'-dicyclohexylurea removed by filtration, and the acyl peptide ester isolated in the usual fashion. (Compare the isolation of products from acylaminoalkyl carbonates, p 194.) An excess of the acylating species is used with

$$R_1CO_2H + H_2NR_2 + C_6H_{11}N=C=NC_6H_{11} \longrightarrow$$
$$R_2CONHR_2 + C_6H_{11}NHCONHC_6H_{11}$$
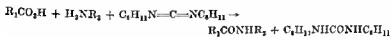
tritylasparagine, tritylglutamine, or tritylisoglutamine, and the reaction in methylene dichloride is allowed to proceed for 13 to 45 hours at —10°. Some of the tritylisoglutamine is cyclized to the tritylpyrrolidone LII.

LII
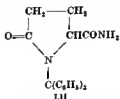
The reaction may be carried out in the presence of water, although better yields usually result in anhydrous solvents such as methylene dichloride or acetonitrile.[213] For example, phthaloyl-L-phenylalanine was coupled with ethyl glycinate in 92% yield in methylene dichloride and in 72% yield in aqueous tetrahydrofuran.[203] Carbobenzoxy-L-serine was coupled with ethyl glycinate in 59% yield in tetrahydrofuran.[204] It was later reported that higher yields were obtained in acetonitrile or methylene dichloride.[213] Khorana used dioxane, tetrahydrofuran, chloroform, and ether as solvents and always obtained acylureas as by-products.[201] With phthaloyl-L-threonine, acylurea formation was observed in dioxane and in tetrahydrofuran, but not in methylene dichloride or acetonitrile.[217] Pyridine and dimethylformamide have also been used as solvents. Low temperatures suppress acylurea formation.[222]

Carbodiimides vary in reactivity and in stability[221] and not all are suitable for peptide synthesis. Although ease of preparation, commercial availability, and stability of N,N'-dicyclohexylcarbodiimide have made it the carbodiimide of choice for peptide synthesis, there are some situations

²²¹ Helferich and Boshagen, *Chem Ber*. **92**, 2813 (1959)

The condensation of carbobenzyloxy-L-asparagine with methyl S-benzyl-L-cysteinate in tetrahydrofuran by means of N,N'-dicyclohexylcarbodiimide gave 39% of methyl carbobenzyloxy-L-asparaginyl-S-benzyl-L-cysteinate, and 26% of the nitrile.[87, 223] When carbobenzyloxyglutamine was substituted for asparagine in this reaction, a 76% yield of peptide resulted and no nitrile was isolated.[223] While yields of 20-30% were obtained in the coupling of equimolar amounts of N-trityl-L-asparagine with amino acid esters at room temperature, the use of excess trityl-L-asparagine at −10° gave yields of 82-96%.[225]

Basic Amino Acids. N,N'-Dicyclohexylcarbodiimide gives satisfactory results with lysine, histidine, and arginine. Ditrityl-L-lysine,[12] ditrityl-L-histidine,[11, 45] dicarbobenzyloxy-L-histidine,[89, 226] dicarbocyclopentyloxy-L-histidine,[15] carbobenzyloxy-im-benzyl-L-histidine,[227-229] carbobenzyloxy-L-arginine,[45, 208] and carbobenzyloxy nitro-L-arginine[216] have been employed for the synthesis of dipeptide intermediates. The scope of the reaction with basic amino acids is better shown by the coupling of carbobenzyloxy-L-arginyl-L-arginine with methyl L-prolyl-L-valinate in 57% yield,[208] of carbobenzyloxy-L-histidyl-L-phenylalanyl-L-nitroarginine with benzyl-L-tryptophylglycinate in 86% yield,[44] and of carbobenzyloxy-L-asparaginyl nitro-L-arginine with methyl L-valyl-L-tyrosyl-L-valyl-L-histidyl-L-prolyl-L-phenylalanyl-L-histidyl-L-leucinate in 70% yield.[230] Lactam formation has been observed with carbobenzyloxynitro-L-arginine in the presence of N,N'-dicyclohexylcarbodiimide.[230a]

Racemization. From 40% to 100% retention of configuration in peptide synthesis has been the experience with N,N'-dicyclohexylcarbodiimide as a reagent. In three experiments in which carbobenzyloxyglycyl-L-phenylalanine was coupled with ethyl glycinate in tetrahydrofuran at room temperature, the DL mixture was obtained in yields of 6.6, 7.6, and 8.2%, respectively. At −5°, only 0.5% of DL mixture was isolated, whereas in methylene dichloride at room temperature 12% was obtained.[231]

Experimental Conditions

Warning: Cases of dermatitis in several laboratories have been ascribed to N,N'-dicyclohexylcarbodiimide; most chemists are not susceptible.

[225] Amiard and Heymès, *Bull. soc. chim. France*, **1957**, 1373.
[226] Sakiyama, Okawa, Yamakawa, and Akabori, *Bull. Chem. Soc. Japan*, **31**, 926 (1958) [*C.A.*, **53**, 19991d (1959)].
[227] Theodoropoulos and Fölsch, *Acta Chem. Scand.*, **12**, 1955 (1958).
[228] Theodoropoulos, *Acta Chem. Scand.*, **12**, 2043 (1958).
[229] The prefix *im* is used to indicate substitution on the imidazole ring. Wieland and Schneider, *Ann.*, **580**, 159 (1953).
[230] Schwyzer, Iselin, Kappeler, Riniker, Rittel, and Zuber, *Helv. Chim. Acta*, **41**, 1273 (1958).
[230a] Bodanszky and Sheehan, *Chem. & Ind.* (*London*), **1960**, 1268.
[231] Anderson and Callahan, *J. Am. Chem. Soc.*, **80**, 2902 (1958).

Amino acids and their esters may be used as the amine component in syntheses with carbodiimides, but, as with other mixed anhydrides, the yields of products are lower with the acids than with the esters.[213]

Since the reaction of the amino acid (or peptide) ester with the α-acylamino acid-carbodiimide adduct is intermolecular whereas the rearrangement of the adduct to the acylurea is intramolecular, the volume of the solvent should be kept to a minimum to favor formation of the peptide intermediate.[201]

In general, for one equivalent of α-acylamino acid there are employed 1.0 to 1.25 equivalents of carbodiimide and 1.0 to 2.0 equivalents of amino acid ester. The reaction is allowed to proceed for 4 to 18 hours at room temperature. Carbobenzyloxy-L-leucyl-L-valine reacts more slowly than carbobenzyloxy-L-leucine.[214]

N,N'-Dicyclohexylcarbodiimide may be prepared by treating N,N'-dicyclohexylthiourea in carbon disulfide with mercuric oxide[215] This reaction is complete in about an hour, and the product is isolated by distillation in 86% yield It is a crystalline solid and may be stored in a refrigerator without change. It is commercially available As a practical point, if the mercuric oxide fails to react with the thiourea, heating the oxide overnight at 70° will activate it.

The requisite dicyclohexylthiourea is prepared by heating cyclohexylamine and carbon disulfide in ethanol containing a small amount of potassium hydroxide.[216] This reaction requires 24 to 48 hours.[213] In this laboratory this reaction time has been shortened by preparing the dithiocarbamic acid cyclohexylammonium salt in ethanol, recovering the salt by filtration, and heating it for 1 hour at 185°. The thiourea, recrystallized from ethanol, is obtained in 77–78% yield by this procedure.

An alternative and very simple procedure involves reaction of N,N'-dicyclohexylurea with pyridine and tosyl chloride.[217-219] By this method, the urea formed in peptide synthesis may be recovered and reused, if desired. By use of 1 equivalent of tosyl chloride the synthesis of 1-cyclohexyl-3-[2-morpholinyl-(4)-ethyl]carbodiimide (LHH) may be achieved. The preparation of carbobenzyloxydipeptide esters in about 60% yield by heating a carbobenzyloxyamino acid and an amino acid ester in tetrahydrofuran in the presence of cyanamide or its substitution products such

²¹³ Okawa, *Bull. Chem. Soc. Japan*, **31**, 98 (1958).

²¹⁴ Schmidt, Hitzler, and Lahde, *Ber*, **71**, 1233 (1938)

²¹⁵ Skita and Rolfes, *Ber*, **53**, 1247 (1920)

²¹⁶ Amard and Heymès, *Bull zoc chim France*, 1956, 1360

²¹⁷ Amard, Heymès, and Velluz, U S pat *2,787,240* (to UCLAF) [*C.A*, **52**, 426f (1958)].

²¹⁸ Amard, Heymès, and Velluz, Fr pat *1,131,266* (to UCLAF) [*Chem Zentr*, **130**, 857 (1959)].

²¹⁹ Fr pat 794,689 (to UCLAF) (1953).

in which the dicyclohexylurea produced as a by-product may not be readily separable from the desired peptide intermediate. In these cases N,N'-dicyclohexylcarbodiimide has been replaced by carbodiimides with solubilizing groups.[213,233] Of these, 1-cyclohexyl-3-[2-morpholinyl-(4)·ethyl]carbodiimide (LIII) and its metho·p-toluenesulfonate are most convenient since they are readily prepared from commercially available chemicals. The acylurea derived from the former carbodiimide is soluble in dilute acids, and that from the latter is soluble in water. Basic carbodiimides such as LIII can be used directly with the amino acid ester

$$C_6H_5CH_2OCONHCH_2CONHCHCO_2H + \overset{\ominus}{Cl}\overset{\oplus}{H_3}NCH_2CO_2C_2H_5 +$$
$$\mid$$
$$CH_2C_6H_5$$

LIII

$$C_6H_5CH_2OCONHCH_2CONHCHCONHCH_2CO_2C_2H_5 + LIII\cdot HCl$$
$$\mid$$
$$CH_2C_6H_5$$
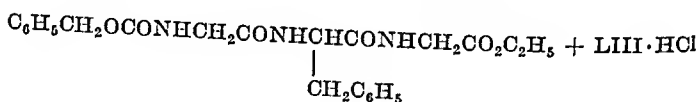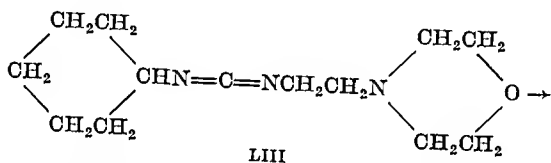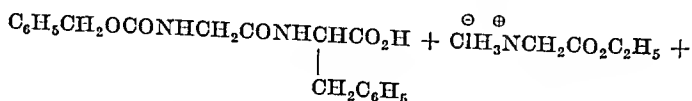
hydrochloride in dioxane. Acetonitrile is the preferred solvent for carbodiimides having a quaternary nitrogen atom. If the hydrohalide salt of an amino acid ester is used, an equivalent amount of triethylamine is added. Carbodiimides having a quaternary nitrogen atom require about 2 days at room temperature for completion of the reaction and tend to give lower yields of product than do the carbodiimides bearing tertiary amine substituents.[233]

Although the p-toluenesulfonate salt of LIII is unchanged after 7 hours in water at 25°, the yield of condensation products with this salt is lower in the presence of water than with either basic or other quaternary carbodiimides. However, phthaloylglycylglycine ethyl ester was prepared in 75% yield in water as the solvent.[233]

Acylureas derived from N,N'-dicyclohexylcarbodiimide are fairly stable and do not react with amino acid esters, at least under mild conditions. However, N-(N-carbobenzyloxyglycyl)-N,N'-di-p-tolylurea reacts readily with cyclohexylamine to give carbobenzyloxyglycine cyclohexylamide and di-p-tolylurea. Other carbodiimides may undergo a similar reaction.[201]

[201] Sheehan and Hlavka, J. Org. Chem., 21, 439 (1956).

saponified by refluxing it for 5 minutes with 8 ml. of 20% methanolic potassium hydroxide and 2 ml. of water The solution is diluted with 30 ml. of water, cooled, and acidified with acetic acid to precipitate the crude acid which, after drying at 100°, weighs 6 5 g. (86%).

The trityl groups are removed by warming the ditrityl peptide for 15 minutes on a water bath with 50% aqueous acetic acid. The solution is then diluted with an equal volume of water, cooled, the triphenylcarbinol removed by filtration, and the solution concentrated. Crystallization is induced by the addition of water. After crystallization from dilute ethanol and drying at 110°, L-histidyl-L-leucine is obtained in 93% yield, m.p. 245° dec., $[\alpha]_p + 13° \pm 1$ ($c = 2\%$, N HCl), $[\alpha]_p -41.5° \pm 2$ ($c = 1\%$, 0 1N NaOH).

Cyclo-glycyl-L-leucylglycylglycyl-L-leucylglycyl.[143] A solution of 500 mg. of glycyl-L-leucylglycylglycyl-L-leucylglycine in a mixture of 100 ml. of water and 400 ml. of methanol is cooled to −3° and 2 g. of N,N'-dicyclohexylcarbodiimide is added. The reaction mixture is allowed to stand for 3 days at −3° and then for 3 days at room temperature. The methanol is removed in vacuum and the excess carbodiimide converted to N,N'-dicyclohexylurea by the addition of 5 ml. of glacial acetic acid. The urea is removed, and the solution is concentrated to about 20 ml. The solution deposits white crystals upon standing. These are collected and recrystallized from hot water to give 190 mg. (47%) of the cyclohexapeptide monohydrate melting with decomposition above 320°.

KETENIMINES

Ketenimines resemble carbodimides An acid will add to a ketenimine LIV to give an isoimide LV which rearranges to a diacylimide LVI.[322-345]

Both the isoimide LV and the diacylimide LVI are acylating agents. Thus N-phthaloylglycyldiphenylacetic acid p-toluide (LVI) reacts with ethyl glycinate to give ethyl phthaloylglycinate and N-(p-tolyl)diphenylacetamide. Other adducts of α-acylamino acids and diphenylketene-p-tolylimine (LIV) behave in the same fashion the reverse cleavage to give a diphenylacetylamino acid ester has not been observed [346] If the ketenimine is added to a mixture of the acid and amine, some of the acylation undoubtedly proceeds via the isoimide.[342, 343, 346]

[342] Morozova and Zhenodarova, *Doklady Akad Nauk S.S.S.R.* 125, 93 (1959) [*C A* 53, 12911a (1959)].
[343] Stevens and Munk, *J Am Chem Soc* 80, 4065 (1958)
[344] Stevens and Munk, *J Am Chem Soc* 80, 4069 (1958)
[345] Stevens, Munk, Freeman, and Gasser, *Abstract No 519 Congress Handbook* XII International Congress of Pure and Applied Chem (March 1951)
[346] Stevens, 130th Meeting, Am Chem Soc, Atlantic City N J Sept 1956, Abstracts, p 9S.

as diethyl-, diphenyl-, or dibenzyl-cyanamide has been reported, but details are lacking.[241]

Experimental Procedures

N,N′-Dicyclohexylcarbodiimide.[237]   *A. Preparation of N,N′-Dicyclohexylurea.*   A mixture of 60 g. of urea and 240 g. of cyclohexylamine is heated under reflux for 20 hours in 480 ml. of isoamyl alcohol. The solution is cooled, the solid collected, washed with diethyl ether, and dried to give 200 g. (89%) of product, m.p. 234°.

With *n*-amyl alcohol as a solvent, yields of 94% of N,N′-dicyclohexylurea were obtained.

B. Preparation of N,N′-Dicyclohexylcarbodiimide.   A solution of 200 g. of N,N′-dicyclohexylurea and 300 g. of *p*-toluenesulfonyl chloride in 600 ml. of pyridine is stirred at 70° for 1 hour and then poured onto 1.5 kg. of ice. The product is taken up in ether. Some insoluble material often is formed at this point; it is probably 1,3-dicyclohexyl-2,4-bis(cyclohexylimino)uretidine. The ether extracts, filtered if necessary, are washed with water, dried, concentrated, and distilled to give 152 g. (82%) of N,N′-dicyclohexylcarbodiimide, b.p. 148–152°/11 mm. The product crystallizes readily, m.p. 35°.

Ethyl Carbobenzyloxyglycyl-L-phenylalanylglycinate.[204]   To a solution of equimolar quantities of carbobenzyloxyglycyl-L-phenylalanine and ethyl glycinate in tetrahydrofuran is added slightly more than one mole equivalent of N,N′-dicyclohexylcarbodiimide. The solution is allowed to stand at room temperature for 4 hours, treated with a small amount of acetic acid to decompose the excess reagent, the insoluble urea removed, and the solvent replaced by ethyl acetate. The ethyl acetate solution is washed with dilute hydrochloric acid and with aqueous potassium bicarbonate, and petroleum ether added. Chilling affords an 87% yield of carbobenzyloxyglycyl-L-phenylalanylglycine ethyl ester; m.p. 118–119°; $[\alpha]_D^{27}$ −13.5° (in ethanol).

L-Histidyl-L-leucine.[11]   To a solution of 1.69 g. of methyl L-leucinate in methylene dichloride is added a solution of 2.5 g. of N,N′-dicyclohexylcarbodiimide in 5 ml. of the same solvent. The solution is cooled to 0°, and 6.4 g. of N,N′-ditrityl-L-histidine is added with stirring. The reaction mixture is allowed to stand overnight at room temperature, 0.5 ml. of acetic acid added to destroy the excess carbodiimide, and the dicyclohexylurea which precipitates (2.5 g.) is removed by filtration. The filtrate is washed with 5N aqueous ammonia and with water, dried, and concentrated to give crude ditrityl-L-histidyl-L-leucine ester which is

[241] Losse and Weddige, *Angew. Chem.*, **72**, 323 (1960).

saponified by refluxing it for 5 minutes with 8 ml of 20% methanolic potassium hydroxide and 2 ml of water The solution is diluted with 30 ml of water, cooled, and acidified with acetic acid to precipitate the crude acid which, after drying at 100, weighs 6 5 g (86%).

The trityl groups are removed by warming the dinitryl peptide for 15 minutes on a water bath with 50% aqueous acetic acid The solution is then diluted with an equal volume of water, cooled, the triphenylcarbinol removed by filtration, and the solution concentrated. Crystallization is induced by the addition of ethanol After crystallization from dilute ethanol and drying at 110°, L-histidyl-L-leucine is obtained in 93% yield, m p. 245° dec , $[\alpha]_p + 13°$ + l ($c = 2\%$, N HCl), $[\alpha]_p -41.5°$ + 2 ($c = 1\%$, $0.1N$ NaOH).

Cyclo-glycyl-L-leucylglycylglycyl-L-leucylglycyl.[242] A solution of 500 mg of glycyl-L-leucylglycylglycyl-L-leucylglycine in a mixture of 100 ml of water and 400 ml of methanol is cooled to $-3°$ and 2 g of N,N'-dicyclohexylcarbodiimide is added. The reaction mixture is allowed to stand for 3 days at $-3°$ and then for 3 days at room temperature. The methanol is removed in vacuum and the excess carbodiimide converted to N,N'-dicyclohexylurea by the addition of 5 ml of glacial acetic acid. The urea is removed, and the solution is concentrated to about 20 ml. The solution deposits white crystals upon standing. These are collected and recrystallized from hot water to give 190 mg. (47%) of the cyclohexapeptide monohydrate melting with decomposition above 320°.

KETENIMINES

Mechanism

Ketenimines resemble carbodiimides. An acid will add to a ketenimine LIV to give an isoimide LV which rearranges to a diacylamide LVI.[243-245]

Both the isoimide LV and the diacylamide LVI are acylating agents. Thus N-phthaloylglycyldiphenylacetic acid p-toluide (LVI) reacts with ethyl glycinate to give ethyl phthaloylglycylglycinate and N-(p-tolyl)diphenylacetamide Other adducts of α-acylamino acids and diphenyl-ketene-p-tolylmine (LIV) behave in the same fashion, the reverse cleavage to a diphenylacetylamino acid ester has not been observed.[246] If the ketenimine is added to a mixture of the acid and amine, some of the acylation undoubtedly proceeds via the isoimide.[243, 244, 246]

[241] Bororova and Zhorodarova, *Doklady Akad Nauk S S S R*, 125, 93 (1959) [C A , 53, 19011c (1959)]

[242] Stevens and Munk, *J Am Chem Soc*, 80, 4065 (1958)

[243] Stevens and Munk, *J Am Chem Soc*, 80, 4069 (1958)

[244] Stevens, Munk, Freeman, and Lapworth, Abstract No 19, *Congress Handbook*, XIV International Congress of Pure and Applied Chem , Zurich, 1955

[245] Stevens, 130th Meeting, Am Chem Soc , Atlantic City, N J , Sept 1956, Abstracts, p 9N

$$\underset{\underset{C_6H_5}{\displaystyle |}}{\overset{\overset{C_6H_5}{\displaystyle |}}{C}}=C=NC_6H_4CH_3\text{-}p \;+\; \underset{\displaystyle LIV}{} \quad \underset{CO}{\overset{CO}{\diagdown}}NCH_2CO_2H \;\rightarrow$$

$$\underset{\underset{C_6H_5}{\displaystyle |}}{\overset{\overset{C_6H_5}{\displaystyle |}}{CHC}}=NC_6H_4CH_3\text{-}p$$

$$O-CCH_2N\overset{OC}{\underset{OC}{}}$$

$$LV$$

$$\overset{C_6H_5}{\underset{C_6H_5}{CHCONC_6H_4CH_3\text{-}p}}$$

$$COCH_2N\overset{OC}{\underset{OC}{}}$$

$$LVI$$

$$\big\downarrow\; H_2NCH_2CO_2C_2H_5$$

$$\overset{CO}{\underset{CO}{\diagdown}}NCH_2CONHCH_2CO_2C_2H_5 \;+\; \overset{C_6H_5}{\underset{C_6H_5}{CHCONHC_6H_4CH_3\text{-}p}}$$
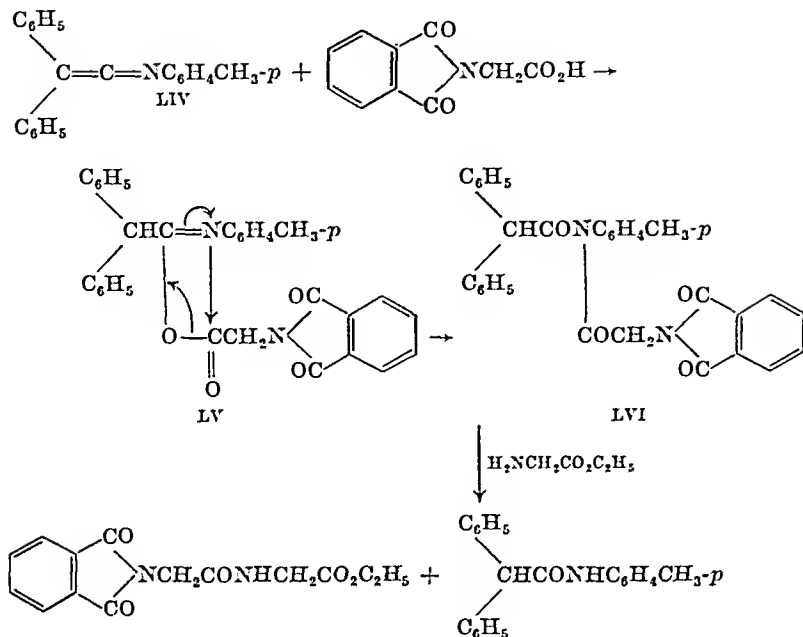
Scope and Limitations

The principal difference between the carbodiimide and the ketenimine method is the stability of the intermediate acylating species. Adducts of diphenylketene-p-tolylimine with phthaloylglycine, carbobenzyloxyglycine, phthaloyl-β-alanine, and phthaloyl-DL-methionine have been isolated, purified, and stored.[244] No evidence of disproportionation has been observed.[246] N-Carbobenzyloxy-S-benzyl-L-cysteine and N-carbobenzyloxy-L-asparagine have been used for peptide synthesis without isolation of the adducts.[244] Phenoxypenicillin has been synthesized by closing the β-lactam ring with pentamethyleneketene cyclohexylimine.[209]

Amine components for peptide synthesis have been ethyl glycinate, ethyl glycylglycinate, ethyl L-leucinate, methyl L-tyrosinate, methyl S-benzyl-L-cysteinate, ethyl p-aminobenzoate,[244] and ethyl DL-threonate.[246,247] The use of sodium salts of amino acids or peptides as the amine component has not been reported, but yields below the 45–77% obtained with esters of the amino acids and peptides in inert solvents would be expected. The presence of water or ethanol has been found to reduce yields because it interferes with the initial addition reaction.[244,246] The effect of water on the amide-forming step has not been determined.

[247] Stevens, U.S. pat. 2,820,781 (to Parke, Davis) [C.A., 52, 10181b (1958)].

The extent to which racemization may occur is not known.

The separation of the N-(p-tolyl)diphenylacetamide from the acylamino peptide ester may present problems. With methyl N-carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosinate the difficulty was overcome by saponifying the peptide ester The ester group of ethyl phthaloylglycyl-L-leucinate was removed by acid hydrolysis.[244] Structural modification of the diphenylketene-p-tolylimine by introduction of solubilizing groups should eliminate some purification problems, as it has with the carbodiimides.[213,233]

Acylated piperazinediones also possess a diacylimine structure. 1,4-Diacetyl-2,5-piperazinedione reacts with methyl and ethyl glycinate to give the corresponding acetic esters,[245] the corresponding 1,4-bis-(N-phthaloylglycyl)-2,5-piperazinedione[136] has not been used for peptide synthesis.

Experimental Conditions

Preparation of the Ketenimine Two convenient methods are available for the synthesis of the ketenimine. Benzilic acid is converted to diphenylketene-p-tolylimine in 50% yield by a four-step synthesis as shown below. The key step in this synthesis is the smooth dehalogenation of the α-chloroimido chloride with sodium iodide in acetone.[246]

$$(C_6H_5)_2CCO_2H \xrightarrow{PCl_5} (C_6H_5)_2COCl \xrightarrow{H_2NC_6H_4CH_3-p}$$
$$OH \phantom{O_2H \xrightarrow{PCl_5} (C_6H_5)_2CO}Cl$$

$$(C_6H_5)_2CCONHC_6H_4CH_3-p \xrightarrow{PCl_5} (C_6H_5)_2C{=\!\!=}C{=\!\!=}NC_6H_4CH_3-p$$
$$Cl \phantom{CONHC_6H_4CH_3-p \xrightarrow{PCl_5} (C_6H_5)_2C{=\!\!=}C}Cl \phantom{{=\!\!=}N}Cl$$

$$\text{NaI in acetone}$$

$$(C_6H_5)_2C{=\!\!=}C{=\!\!=}NC_6H_4CH_3-p$$
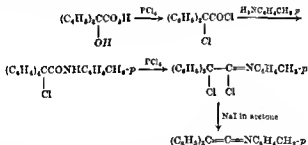
The ketenimine is obtained as the yellow crystalline monomer It reacts only slowly with aqueous acetone but is rapidly hydrolyzed in the presence of hydrochloric acid.

The same ketenimine may be prepared from diphenylacetic acid in a three-step synthesis proceeding through N-(p-tolyl)diphenylacetamide and N-(p-tolyl)diphenylacetimido chloride. Dehydrochlorination of the latter compound with triethylamine gives the ketene in 65% yield based on amide.[250]

[244] Petrova, Akimova, and Ostroslov, Zhur Obshchei Khim., 24, 2230 (1954) [C A , 50, 359g (1956)]

[245] Stevens and French, J. Am Chem Soc , 75, 657 (1953)

[246] Stevens and French, J. Am. Chem. Soc , 76, 4398 (1954).

$$(C_6H_5)_2CHCONHC_6H_4CH_3\text{-}p \xrightarrow{\text{PCl}_5} (C_6H_5)_2CHC\text{---}NC_6H_4CH_3\text{-}p$$

$$\downarrow$$

$$Cl$$

$$\downarrow (C_2H_5)_3N$$

$$(C_6H_5)_2C\text{==}C\text{==}NC_6H_4CH_3\text{-}p$$
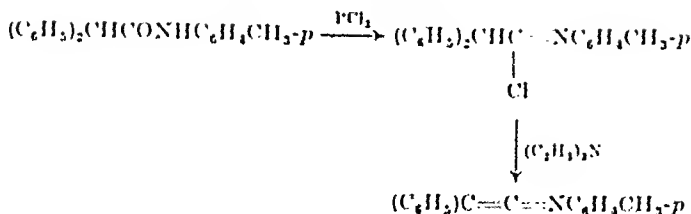
Diphenylketene-*p*-tolylimine is the most suitable ketenimine thus far explored for peptide synthesis. Ease of preparation from available starting materials, stability, and cleavage of the intermediate diacylimide in the desired direction are the principal factors for this choice.

Preparation of the Mixed Imide. To prepare the diacylimide, a solution of one equivalent of diphenylketene-*p*-tolylimine in an inert solvent such as benzene, tetrahydrofuran, or methylene dichloride is refluxed with one equivalent of an α-acylamino acid until the yellow color of the ketenimine is discharged. Up to 23 hours are needed. At room temperature, 2 or 3 days are required. Hydroxylated solvents result in lowered yields. The adducts may be used without isolation, or may be isolated by evaporation of the solvent and recrystallization of the residue.[244] Although diacylimides are subject to alcoholysis,[243] the adduct may be recrystallized from ethanol.

Amide Formation. A solution of one equivalent of ketenimine with one equivalent of an α-acylamino acid or of the preformed adduct prepared from them is treated with one equivalent of amino acid or peptide ester in a solvent such as benzene, methylene dichloride, or tetrahydrofuran. The hydrochloride of the amino acid ester may be used if at least one equivalent of triethylamine is added. The reaction is usually complete after heating under reflux for 2 or 3 hours. However, with ethyl *p*-aminobenzoate a reaction time of 44 hours was necessary.[244, 247] If the α-acylamino peptide ester precipitates from the reaction mixture it may be recovered by filtration and washed with water to remove triethylamine hydrochloride, if present. If the product does not precipitate, transfer to another solvent may be attempted or the crude reaction mixture may be employed in the next step.

Experimental Procedures

N-Phthaloylglycyldiphenylacetic Acid *p*-Toluide.[244] A solution of 2.0 g. (7.1 mmoles) of diphenylketene-*p*-tolylimine and 1.5 g. (7.1 mmoles) of phthaloylglycine in 35 ml. of benzene is heated under reflux until the yellow ketenimine color is discharged. The solution is then evaporated to dryness in vacuum and the solid residue, m.p. 168–170°, is

recrystallized from hexane-acetone to yield 3.2 g (92%) of adduct, m.p. 179.5–180 5°.

Ethyl Phthaloylglycylglycylglycylglycinate.[244] To a solution of 1.0 g (2.1 mmoles) of N-phthaloylglycylglycyldiphenylacetic acid *p*-toluide in 10 ml. of methylene dichloride is added, with stirring, 0 4 g. (2.1 mmoles) of glycylglycine ethyl ester hydrochloride and 0.5 ml. (3.3 mmoles) of triethylamine. The mixture is stirred and heated for 9 hours, during which time the amount of suspended solid increases. The white solid is then separated by filtration, washed with water, and dried to give 0.35 g. (49%) of the tripeptide, m p 221–222°. Recrystallization from water raises the melting point to 225–226°

Ethyl Phthaloylglycyl-*p*-aminobenzoate.[244] To 15 ml. of methylene dichloride are added 1 09 g. (3.5 mmoles) of diphenylketene-*p*-tolylimine, 0 8 g (3 9 mmoles) of phthaloylglycine and 0 6 g (3 6 mmoles) of ethyl *p*-aminobenzoate. The mixture is heated under reflux for one hour and forty minutes, although the yellow ketenimine color is completely discharged after fifteen minutes The solution is evaporated to dryness in vacuum and the solid residue recrystallized from benzene to give 0.95 g. (77%) of dipeptide, m.p. 204 0–205 5°.

KETENES AND ISOCYANATES

Both ketenes and isocyanates react with carboxylic acids by 1,2 addition followed by rearrangement to mixed anhydrides [260] However, these
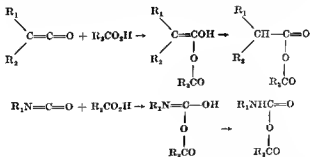
mixed anhydrides have not yet been used for peptide synthesis. With ketene the mixed anhydride is the same as that obtained from the more readily accessible acetyl chloride, and with diphenylketene the anhydride is that obtained more conveniently from diphenylacetyl chloride.

Acyl carbamates derived from isocyanates have been used for the synthesis of amides but not of peptides [261] A useful peptide synthesis

---

[241] Naegeli and Tyabji, *Helv Chim Acta*, **17**, 931 (1934). **18**, 142 (1935).

has been developed using certain isocyanates obtained from esters of amino acids. An acylamino acid and such an isocyanate react to give an anhydride which rearranges to a peptide.[117, 252] The rearrangement is base catalyzed.

$$C_6H_5CH_2OCONHCH_2CO_2H + O=C=NCH_2CO_2CH_3 \rightarrow$$

$$C_6H_5CH_2OCONHCH_2COOCONHCH_2CO_2CH_3 \xrightarrow{\text{Pyridine}}$$

$$C_6H_5CH_2OCONHCH_2CONHCH_2CO_2CH_3 + CO_2$$

ACETYLENIC ETHERS

Organic acids add to acetylenic ethers to give intermediates LVII which behave as mixed anhydrides, for a second mole of acid may be added to give an anhydride and an alkyl acetate. The same products would result if the acid anion attacked the carbonyl group of the adduct.[253, 254]

$$HC≡COCH_3 + R_1CO_2H \rightarrow H_2C=COCH_3 \xrightarrow{H_2NCHRCO_2CH_3} R_1CONHCHRCO_2CH_3$$

$$+ CH_3CO_2CH_3$$

$$R_1CO_2H$$

$$(R_1CO)_2O + CH_3CO_2CH_3$$

An amide would be expected as the product from the reaction of the adduct with an amine. Arens realized this expectation by preparing peptides from methyl ethinyl ether with esters of amino acids.[255, 256] The by-product is methyl acetate.

The method has been used to prepare di- and tri-peptides in which the acylating species have been glycine, alanine, β-alanine, valine, leucine, isoleucine, proline, S-benzylcysteine, phenylalanine, tryptophan, tyrosine, lysine, and glutamic acid. Yields have ranged from 34% to 100%. No pure products could be isolated in attempts to prepare ethyl carbobenzyloxy-DL-serylglycinate or ethyl carbobenzyloxy-L-tryptophylglycinate.[257]

Phthaloylglycine reacts with glycine ester in water in the presence of ethyl ethinyl ether to give ethyl phthaloylglycylglycinate and a neutral

[251] Goldschmidt and Wick, *Ann.*, **575**, 217 (1952).
[252] Arens and Modderman, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **53**, 1163 (1950) [*C.A.*, **45**, 6152d (1951)].
[253] Eglinton, Jones, Shaw, and Whiting, *J. Chem. Soc.*, **1954**, 1860.
[254] Arens, *Rec. trav. chim.*, **74**, 769 (1955).
[255] Arens, *Festschr. Arthur Stoll*, **1957**, 468 [*C.A.*, **52**, 15414c (1958)].
[256] Panneman, Marx, and Arens, *Rec. trav. chim.*, **78**, 487 (1959).

product assigned structure LVIII. The latter product reacts with ethyl glycinate in dioxane at 50° to give 80% of ethyl phthaloylglycylglycinate.[258]

LVIII

Although mercuric salts accelerate peptide synthesis with acetylenic ethers, less pure products are obtained than in their absence.[257]

In the synthesis of peptides by this method, racemization has been encountered but can be decreased considerably by the selection of suitable reaction conditions.[258] Carbobenzyloxyglycyl-L-phenylalanine reacts with ethyl glycinate hydrochloride in the presence of ethyl ethynyl ether in boiling ethyl acetate to give a product which is racemized to the extent of 45%. When ethyl glycinate is substituted for the hydrochloride, no racemization is observed in the product. However, the recovered carbobenzyloxyglycyl-L-phenylalanine is racemized to a slight extent. Carbobenzyloxyglycyl-L-phenylalanine and carbobenzyloxyglycyl-L-leucine are racemized by refluxing with ethyl ethynyl ether in ethyl acetate.[257]

Carbodimides, keteminines, and acetylenic ethers have all been used in the total synthesis of penicillin V The carbodimide method gave the best yield.[264] N,N'-Dicyclohexylcarbodimide is commercially available and keteminines are readily prepared by newly developed methods, but acetylenic ethers are not so accessible. The method of preparation of ethyl ethynyl ether appearing in *Organic Syntheses*[260] involves the reaction of sodium amide with chloroacetal The reaction has been characterized as hazardous unless the directions are closely followed,[261] and it does not always give reproducible results. More satisfactory routes for the synthesis of ethyl ethynyl ether appear to be the treatment of chloroacetal with potassium persulfate and then potassium hydroxide,[262],[263] or the bromination of ethyl vinyl ether followed by dehydrohromination.[263],[264]

Experimental Conditions

Three general procedures for peptide synthesis with acetylenic ethers have been developed. In the first, an amino acid ester is powdered with

[258] Sheehan and Hlacks, *J Org Chem*, **23**, 635 (1958)

[259] Arens, *Angew Chem*, **70**, 631 (1958)

[260] Jones, Eglinton, Whiting, and Shaw, *Org Syntheses*, **34**, 46, 1934

[261] Van Dorp, Arens, and de Boer, *Rec trav chim*, **72**, 753 (1953)

[262] Van Dorp, Arens, and Stephenson, *Rec trav chim*, **70**, 253 (1951)

[263] Arens, *Rec trav chim*, **74**, 271 (1955)

[264] Nazarov, Kraonaya, and Vinogradov, *Zhur. Obshchei Khim*, **28**, 460 (1958) [*C A*, **52**, 13611g (1958)]

a 5–10% excess of an α-acylamino acid and four or five molar equivalents of an acetylenic ether added. If a spontaneous reaction does not occur, a drop of water or of N hydrochloric acid is added to initiate the reaction. This procedure is rapid, but it does not give the best yields.[257]

The second method differs only in that a solvent is employed. Ethyl acetate containing 0.5% water is greatly superior[257] to other solvents such as diethyl ether, chloroform, methylene dichloride, dimethylformamide, dioxane, nitromethane, and ethanol,[265, 266] which have been used. Acetonitrile is sometimes a good solvent. Anhydrous ethyl acetate requires longer heating than moist ethyl acetate and the products are less pure. The reaction mixture is heated under refluxing conditions until solution occurs, but not longer than 3 hours. Closed reaction vessels have been used in some instances because of the low boiling point of the acetylenic ether.

When racemization is a problem, a third method is employed. The free amino acid ester is heated under reflux with a slight excess of α-acylamino acid and four to five equivalents of ethyl ethinyl ether in moist ethyl acetate for $1\frac{1}{2}$ to 2 hours.

Experimental Procedures

Benzyl Carbobenzyloxy-L-valyl-L-tyrosyl-L-prolinate.[257] A mixture of 10.4 g. of carbobenzyloxy-L-valyl-L-tyrosine, 5.8 g. of L-proline benzyl ester hydrochloride, and 7 g. of ethyl ethinyl ether in 200 ml. of moist ethyl acetate (5% water) was heated under reflux for $2\frac{1}{2}$ hours. The mixture was cooled for 18 hours and filtered to give 8.9 g. (61%) of carbobenzyloxytripeptide ester, m.p. 186–188°, $[\alpha]_D^{21.5}$ −40.6° ($c = 1\%$, pyridine).

Ethyl N-Carbobenzyloxy-S-benzyl-L-cysteinylglycinate.[266] An ethyl acetate solution of N-carbobenzyloxy-S-benzyl-L-cysteine, ethyl glycinate, and ethyl ethinyl ether in the molar ratio of 1:1:2 was heated at 60° for 3 hours. The reaction mixture was then washed successively with $2N$ hydrochloric acid, water, $2N$ sodium carbonate, and water. The ethyl acetate solution was dried and concentrated under reduced pressure, and the residue crystallized from ethyl acetate and petroleum ether to give 90% of product, m.p. 98°, $[\alpha]_D^{20}$ −26.5° ($c = 6\%$, glacial acetic acid).

Cyclo-glycyl-L-leucylglycylglycyl-L-leucylglycyl.[242] To a solution of 500 mg. of glycyl-L-leucylglycylglycyl-L-leucylglycine in 500 ml. of methanol at 20° was added 1.75 ml. of ethyl ethinyl ether. The reaction mixture was allowed to stand for 1 week at room temperature and was then heated and stirred for 3 hours at 40–45°. The methanol solution

[265] Arens, U.S. pat. 2,793,204 (to N.V. Organon) [C.A., 51, 16522i (1957)].
[266] Brit. pat. 791,791 (to N.V. Organon) [C.A., 52, 16240i (1958)].

was concentrated in vacuum to a small volume and diluted with 15 ml. of water The white crystalline precipitate that separated on standing was collected and recrystallized from hot water to give 52 mg. of material, dec. > 320°. It was insoluble in 2N hydrochloric acid or sodium hydroxide as well as in most organic solvents, and it gave a negative ninhydrin test. The yield of cyclohexapeptide monohydrate was 11.2%.

ETHYL α-CHLOROVINYL ETHER AND α,α-DICHLORODIETHYL ETHER

An α-acylamino acid and the ester of an amino acid hydrochloride will react in the presence of ethyl α-chlorovinyl ether (LIX) or α,α-dichloro-diethyl ether (LX) to give an acyldipeptide ester, hydrogen chloride, and ethyl acetato.[287]

$$\underset{\substack{\text{LIX}}}{\text{H}_2\text{C}=\text{COC}_2\text{H}_5} \qquad \underset{\substack{\text{LX}}}{\overset{\text{Cl}}{\underset{\text{Cl}}{\text{CH}_3\text{COC}_2\text{H}_5}}} \qquad \underset{\substack{\text{LXI}}}{\overset{\text{Cl}}{\underset{\text{OCOCHRNHCOR}}{\text{CH}_3\text{COC}_2\text{H}_5}}}$$
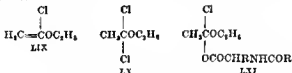
The reaction is believed to proceed through the hypothetical intermediate LXI which decomposes to give the α-acylamino acid chloride, the active acylating species. The acid chloride may be isolated if the amino acid ester hydrochloride is not added to the reaction mixture.

The requisite α-chloro ethers LIX and LX are obtained by addition of one or two equivalents of hydrogen chloride, respectively, to ethyl ethinyl ether. In general, better yields result and shorter reaction times are required with the dichloro ether LX than with the monochloro ether LIX. When using the monochloro ether superior results are obtained if the reaction mixture is allowed to stand at room temperature overnight before heating under reflux. For example, ethyl carbobenzyloxy-glycylglycinate was prepared in 60% yield when the reactants were heated immediately after mixing, and in 91% yield when they were allowed to stand at room temperature before heating. At room temperature the hydrogen chloride liberated during peptide synthesis probably converts some of the α-chlorovinyl ether to the dichloro ether, so that part of the reaction then proceeds via the dichloro ether. The correlation between reaction time and refractive index of the ether supports this proposition.

Scope and Limitations

Both the carbobenzyloxy and phthaloyl derivatives of glycine, L-alanine, L-leucine, L-phenylalanine, and carbobenzyloxy-L-valine have been used as the acid component. The amine component has been ethyl

[287] Healings and Arens, *Rec. trav. chim.*, **76**, 582 (1957).

glycinate, ethyl L-phenylalaninate, and ethyl glycylglycinate. Satisfactory yields with carbobenzyloxy amino acids were obtained even though their acid chlorides decompose when heated. It is unlikely, however, that either carbo-*t*-butoxy or trityl amino acids will survive an attempt at peptide synthesis using the α-chloro ether method.

The reaction of an α-acylamino acid chloride with the ester of an amino acid hydrochloride by heating under refluxing conditions in ethyl acetate appears to be general.[267]

Although optically pure carbobenzyloxy and phthaloyl dipeptide esters were prepared by the α-chloro ether procedure, racemization would probably be encountered if an acyldipeptide were used as the acid component.

Experimental Conditions

A suspension of one equivalent of the ester of an amino acid hydrochloride in ethyl acetate is allowed to react with 1.3 molar equivalents of the carbobenzyloxy- or phthaloyl-amino acid and three to four molar equivalents of ethyl α-chlorovinyl ether for 12 to 24 hours at room temperature, and is then heated under refluxing conditions. Generally completion of the reaction is indicated by formation of a clear solution. If solution does not occur after 9 hours, the reaction is stopped.

The procedure using α,α-dichlorodiethyl ether differs only in the shorter reaction time, $\frac{1}{2}$ to $1\frac{1}{4}$ hours.

The reaction may be conducted without a solvent by intimately mixing equivalent amounts of the acid and amino acid ester hydrochloride, adding three to four equivalents of α-chlorovinyl ether and heating to 80–110° for 10 to 20 minutes. A vigorous reaction occurs. Ethyl acetate is then added and the mixture heated under refluxing conditions for $\frac{1}{2}$ to 1 hour.

The product is isolated by washing the reaction mixture with water and with aqueous potassium carbonate, drying, diluting with hexane, and chilling.

α-ACYLAMINO ACID PHENOLIC ESTERS

Several phenolic esters of phthaloylglycine have been condensed with ethyl glycinate in boiling benzene to give ethyl phthaloylglycylglycinate.[268]

Phthaloylglycine Ester	Reaction in 20 Minutes, %	Phth.Gly.Gly.OC$_2$H$_5$ Isolated, %
Phenyl	27	3
Thiophenyl	48	31
o-Nitrophenyl	90	76
m-Nitrophenyl	98	83
p-Nitrophenyl	95	75

[268] Bodanszky, *Nature*, **175**, 685 (1955).

Scope and Limitations

Two methods of synthesis of phenyl esters of α-acylamino acids have been used, namely the reaction of a mixed anhydride of an α-acylamino acid with a phenol and the reaction of an α-acylamino acid with an acylated phenol. The first procedure adds an extra step since the α-acylamino acid anhydride could itself be used as an acylating agent

Acid chlorides,[269,276] sulfuric acid anhydrides,[269] mixed carbonates,[269] phosphorus oxychloride,[27] thioglycolic esters,[271] and dicyclohexyl-carbodiimide[273,273] have been used to couple the α-acylamino acid and phenol. However, an attempt to condense the α-acylamino acid with salicylamide using dicyclohexylcarbodiimide failed.[274] There are several advantages in the use of phenolic esters for forming peptide bonds (1) *the phenolic esters, particularly the p-nitrophenyl esters, are stable crystalline compounds which may be stored until needed,* (2) the phenyl esters permit the use of free amino acid rather than its ester and thus eliminate the need for purification of the product by countercurrent distribution, and (3) the group protecting the α-amino function can be removed from the peptide without affecting the phenolic ester   The last advantage is especially useful in the synthesis of cyclic peptides. The conversion of α-acylamino acids to phenolic esters with carbodiimides avoids contamination of the final peptide with the N-acylurea which might be formed If the carbodiimide were used directly for peptide synthesis.

The α-acylamino acid may be converted to a phenolic ester in one step by reaction with a triaryl phosphite[275,276] or a diaryl sulfite.[276a,277] It is believed that the reaction between an acid such as LXII and diphenyl sulfite LXIII proceeds as shown. This formulation accommodates the observation that carbobenzyloxyglycine and diphenyl sulfite in the presence of a five-fold excess of p-nitrophenol in pyridine gave 83% of p-nitrophenyl carbobenzyloxyglycinate and 8% of phenyl carbobenzyl-oxyglycinate.[274] In the accompanying formulas (see equation at top of p. 224) X is preferably a para nitro group, but it may be a methyl-sulfonyl, cyano, or other negative substituent.

Negatively substituted symmetrical triaryl phosphites react with two

[269] Rudancky, *Acta Chim. Acad. Sci. Hung.*, **10**, 335 (1957) [*C A.*, **52**, 6288 (1958)]

[270] Wieland and Jaenicke, *Ann.*, **549**, 125 (1958)

[271] Schwyzer, *Ger pat.*, 857,843 (to Ciba) [*C A.*, **52**, 1461i (1959)].

[272] Elliott and Kuntz, *Proc. Biochem Soc*, **66**, 49p (1957)

[273] Rothe and Kuntz, *Ann.*, **609**, 88 (1957)

[274] Kerr and Niemann, *J. Org Chem*, **23**, 893 (1958)

[275] Belgian pat. 553,952 (to Ciba) (1957).

[276] Iselin, Rittel, Sieber, and Schwyzer, *Helv Chim Acta*, **40**, 373 (1957)

[276a] Schwyzer, Iselin, Risher, Rittel, and Sieber, *U S. pat.* 2,817,502 (to Ciba)

[277] Schwyzer and Sieber, *Chimia (Switz.)*, **10**, 255 (1956).

$$RCOO^- + \underset{\substack{| \\ OC_6H_4X}}{\overset{\substack{OC_6H_4X \\ |}}{SO}} \rightarrow \left[\underset{\substack{| \\ O}}{\overset{\substack{OC_6H_4X \\ |}}{RCO-S-O^-}} \underset{OC_6H_4X}{} \right] \rightarrow$$
LXII   LXIII

$$\overset{O}{\underset{|}{RC}}-O-\overset{O}{\underset{|}{S}}-OC_6H_4X + XC_6H_4O^- \rightarrow$$

$$RCO_2C_6H_4X + SO_2 + {}^-OC_6H_4X + [{}^-O-S-OC_6H_4X]$$
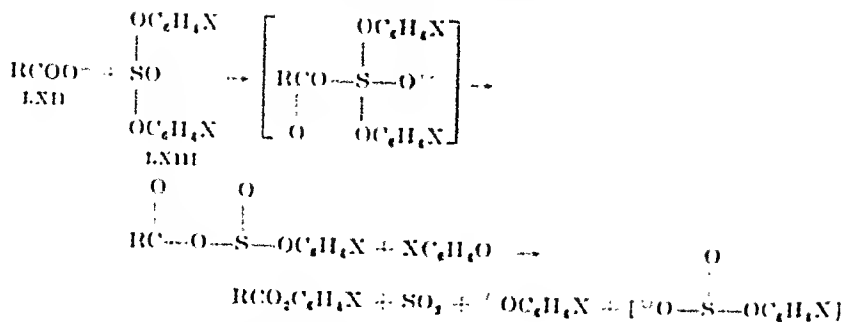
moles of an α-acylamino acid to give the acyl ester and presumably a monoaryl phosphorous ester.[276]

It was noted previously (p. 223) that phenolic esters are particularly useful for the synthesis of cyclic peptides. Gramicidin S was synthesized from trityl-L-valyl-tosyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-prolyl-L-valyl-tosyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-proline by conversion to the p-nitrophenyl ester with di-p-nitrophenyl sulfite, detritylation with trifluoroacetic acid, cyclization in hot pyridine, and detosylation with sodium in liquid ammonia.[278-281] A number of cyclohexapeptides have been similarly prepared.[146,149] The tendency of peptides having an odd number of amino acids to double on cyclization was utilized in synthesizing ditosyl gramicidin S in 31% yield from L-valyl-S-tosyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-proline p-nitrophenyl ester.[282]

A series of cyclopolycaprolactams was prepared from the nitrophenyl and dinitrophenyl esters of the peptides by warming them in dimethylformamide or in pyridine.[273]

$$\left[\underset{\substack{| \\ [CO(CH_2)_5NH]_nH \\ R = H \text{ or } NO_2}}{\overset{\substack{NH(CH_2)_5CO_2 \quad R \\ }}{}} \right] \longrightarrow \underset{\substack{| \\ [CO(CH_2)_5NH]_n \\ n = 1-5}}{\overset{NH(CH_2)_5CO}{}} + HO-\underset{NO_2}{\overset{R}{\bigcirc}}$$
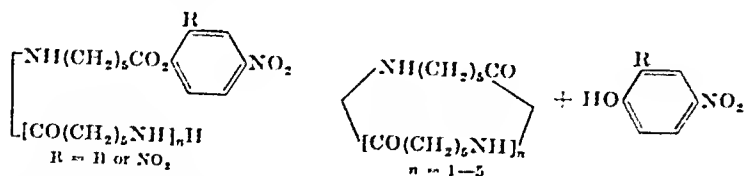
Carbobenzyloxy-S-benzyl-L-cysteine p-nitrophenyl ester reacts with L-tyrosine in aqueous tetrahydrofuran to give 9% of acyldipeptide, whereas the reaction with ethyl L-tyrosinate followed by hydrolysis gives the same acyl dipeptide in 83% yield. Phthaloylglycine p-nitrophenyl ester reacts with glycine in aqueous dimethylformamide to give 74% of phthaloylglycylglycine; this is more typical of the yields ordinarily

[276] Schwyzer and Sieber, Angew. Chem., 68, 518 (1956).
[280] Schwyzer and Sieber, Helv. Chim. Acta, 40, 624 (1957).
[281] Brit. pat. 836,725 (to Ciba) (1960).
[282] Brit. pat. 836,726 (to Ciba) (1960).

obtained.[268] Substitution of glycine amide for glycine in the above reaction leads to a 75–80% yield of phthaloylglycylglycylamide.[263]

Glycine phenyl ester reacts with alanine (configuration not specified) in the presence of bicarbonate, but not in the presence of pyridine. An oxazolidone intermediate was postulated to explain these results.[276]

The formation of 2,4-dinitrophenylamino acids from 2,4-dinitro-fluorobenzene and the amino acid in aqueous ethanol in the presence of sodium bicarbonate is accompanied by 2,4-dinitrophenyl dimers and higher polymers as by-products.[256] These results suggest that the 2,4-dinitrophenylamino acids LXIV form with 2,4-dinitrofluorobenzene a mixed anhydride LXV which reacts further with another molecule of amino acid. With ε-aminocaproic acid, evidence for the formation of a dinitrophenyl pentapeptide was obtained. This reaction is not of preparative

$$2,4\text{-}(O_2N)_2C_6H_3F + H_2NCH_2CO_2H \xrightarrow{NaHCO_3}$$

$$2,4\text{-}(O_2N)_2C_6H_3NHCH_2CO_2H \xrightarrow[2,4\text{-}(O_2N)_2C_6H_3F]{NaHCO_3}$$
$$\text{LXIV}$$

$$2,4\text{-}(O_2N)_2C_6H_3NHCH_2CO_2C_6H_3(NO_2)_2\text{-}2,4 \xrightarrow{H_2NCH_2CO_2H}$$
$$\text{LXV}$$

$$2,4\text{-}(O_2N)_2C_6H_3NHCH_2CONHCH_2CO_2H$$

value. No reaction occurred between the lithium salt of carbobenzyl-oxyglycine and 2,4-dinitrofluorobenzene or picryl chloride.[56]

Both glycyl-L-alanine[269] and carbobenzyloxy-β-benzyl-L-aspartyl-L-arginine[272] have been prepared with retention of configuration, but these examples do not constitute proof that acylation will invariably proceed without racemization. The *p*-nitrophenyl ester obtained from the anhydride of carbobenzyloxyglycyl-L-phenylalanine and sulfuric anhydride had a small optical rotation, but it gave a DL product on reaction with glycine.[80]

[263] Bodánszky, Szelke, Tomorkeny, and Weisz, *Acta Chim Acad Sci Hung*, **11**, 179 (1957), *Chem & Ind (London)*, **1955**, 1517

[264] Heikens, Hermans, and van Velden, *Nature*, **174**, 1187 (1954).

Experimental Conditions

Preparation of Phenolic Esters from α-Acylamino Acids. One mole of α-acylamino acid or α-acylamino peptide is treated with 1.0 to 1.5 moles of diaryl sulfite or 0.50 to 0.56 mole of triaryl phosphite in the presence of 2 moles of pyridine at room temperature to 50° for 2 to 3 hours. The higher temperature is employed when the reaction mixture has been diluted with ethyl acetate or chloroform.[276]

Preparation of Phenolic Esters from α-Acylamino Acid Anhydrides. To the mixed anhydrides of α-acylamino acids with acid chlorides or mixed carbonates, the requisite phenol is added in the presence of N-ethylpiperidine or triethylamine in tetrahydrofuran or chloroform.[269, 273] Phenyl hippurate is produced in unstated yield by warming S-hippurylthioglycollic acid with phenol at 80° for 4 hours.[271]

Formation of the Peptide Bond. A variety of solvents has been employed for the aminolysis. Ethyl acetate was superior to tetrahydrofuran in the reaction of the p-nitrophenyl ester of phthaloylglycine with ethyl glycinate.[283] Reaction times have varied from a few minutes in the reaction between the 2,4-dinitrophenyl ester of phthaloylglycine and ethyl glycinate in dioxane to 3 days in the reaction of the p-nitrophenyl esters of phthaloylglycine and ethyl glycinate in benzene at room temperature. In the latter instance, the yield of ethyl phthaloylglycylglycinate was 76%.[269] The same reaction carried out overnight in ethyl acetate instead of benzene gave a 96% yield.[283]

Experimental Procedures

p-**Nitrophenyl Carbobenzyloxyglycinate.**[276] A solution of 209 mg. (1 mmole) of carbobenzyloxyglycine in 2 ml. of ethyl acetate and 0.61 ml. (2 mmoles) of pyridine was treated with 324 mg. (1 mmole) of di-p-nitrophenyl sulfite. The solution was held at 50° for 3 hours, cooled to 0°, washed with $2N$ HCl, saturated aqueous sodium bicarbonate, and water, dried, and the solvent evaporated to give a crystalline residue (328 mg., m.p. 119–121°) which was recrystallized from ethanol to give 315 mg. (95%) of the ester, m.p. 124–125°.

Cyclo-glycylglycyl-DL-phenylalanylglycylglycyl-DL-phenylalanyl.[149] A solution of 4.1 g. of the p-methanesulfonylphenyl ester of glycylglycyl-DL-phenylalanylglycylglycyl-DL-phenylalanine hydrochloride in 80 ml. of dimethylformamide and 4 ml. of acetic acid was added dropwise to 820 ml. of pyridine at 95° during 5 hours. The reaction mixture was stirred for an additional 2 hours at the same temperature and the solvents were then removed in vacuum. The residue was dissolved in 1:1 methanol-water and passed through strongly acidic and basic ion exchange

resins. The columns were washed with the same solvent, and the combined eluates and washings were concentrated in vacuum to dryness. *The residue was triturated with acetone and filtered to give 380 mg (13%)* of product. The crude product was dissolved in a large volume of aqueous methanol, concentrated, and allowed to crystallize. It was recrystallized from a small volume of acetic acid to give colorless needles, m.p. about 300° with decomposition.

N-Carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosine.[253] To a solution of 0.47 g (0.001 mole) of the p-nitrophenyl ester of N-carbobenzyloxy-S-benzyl-L-cysteine in 3 ml of tetrahydrofuran were added 0.25 g (0.011 mole) of ethyl L-tyrosinate hydrochloride and 0.15 ml of triethylamine. The solution soon became yellow. On the next day, 20 ml of water was added. The oil that precipitated was dissolved in 1 ml of 2N aqueous sodium hydroxide and 1 ml of methanol and acidified with N hydrochloric acid after 1 hour. The precipitate was dissolved in aqueous sodium bicarbonate, filtered, and again acidified with N hydrochloric acid. The product, 0.43 g (84.5%), m.p. 196–198°, was recrystallized from ethanol to give 80% over-all of the acyl peptide, m.p. 197–200°, [α]_D −6.4 [c = 14% (0.5 N-KHCO₃)]

Phthaloylglycylglycinamide.[253] To a solution of 1.63 g (0.005 mole) of p-nitrophenyl phthaloylglycinate in 10 ml of dimethylformamide were added 0.7 ml (0.005 mole) of triethylamine and 0.55 g (0.005 mole) of glycinamide hydrochloride. The mixture was heated for 50 minutes on a steam bath, cooled, and 30 ml of water was added to precipitate the product which was collected, washed with water, and dried to give 0.95 g. (75%) of acylpeptide amide, m.p 235° with decomposition. Recrystallization of 0.15 g of this material from 45 ml of ethanol gave 0.12 g. of amide, m.p. 250–252°.

BRENNER'S METHOD

An interesting method of forming peptide bonds was described by Brenner in 1955,[283–287] and a summary of the work has appeared.[288] (See also ref. 149a, pp. 157–261.)

The perchlorate of O-glycylsalicylamide (LXVII) rearranges in aqueous potassium bicarbonate to salicylglycinamide (LXVIII). The same perchlorate LXVII on solution in water rearranges to the imidazolone LXVI To account for these results, the very plausible assumption was

²⁸³ Brenner, *14th Congr. IUPAC*, Zurich, July 21–25, 1955 Cf *Chem Eng News*, **33**, 3490 (1955)

²⁸⁴ Brenner, Zimmermann, Wehrmuller, Quitt, and Photaki, *Experientia*, **11**, 397 (1955).

²⁸⁵ Brenner, *Angew Chem*, **67**, 733 (1955)

²⁸⁶ Brenner, Zimmermann, Wehrmuller, Quitt, Hartmann, Schneider, and Beglinger, *Helv Chim Acta*, **40**, 1497 (1957)

made that the amino groups reacted with sterically adjacent carbonyl groups to give a tricyclic intermediate LXIX.

The rearrangement in basic solution may proceed via bicyclic intermediates.[141, 289] Ring closure between the amide nitrogen and ester

LXVI   LXVII   LXVIII

LXIXa LXIX   LXIXb
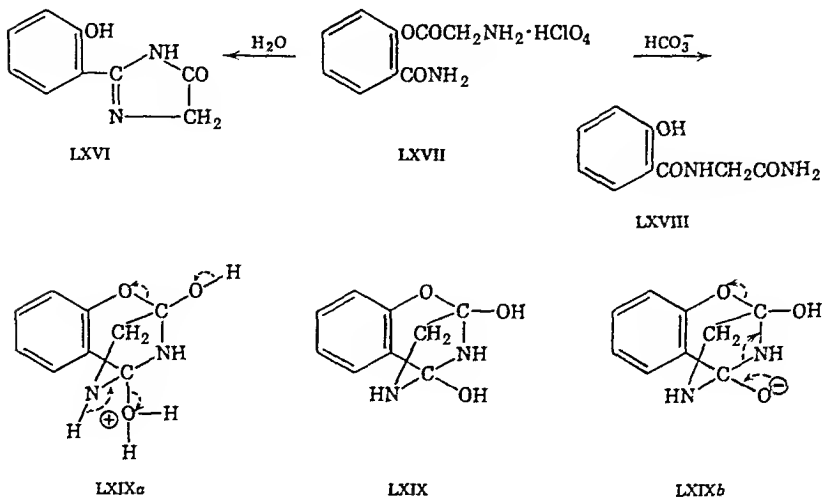
carbonyl components of LXVII followed by scission of the labile phenolic oxygen bond would lead to a diacylimide LXX, a type which Wieland[290]

LXX
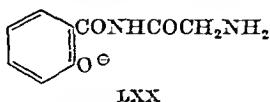
has shown rearranges further to give, in this case, the observed salicylglycylamide. Later work has given results difficult to reconcile with this proposed mechanism.[288, 291]

A related rearrangement is that of O-acetyl-N-benzoylsalicylamide (LXXI) and O-benzoyl-N-acetylsalicylamide (LXXII) to N-benzoylsalicylamide (LXXII) on treatment with aqueous base.[292] (Equations on p. 229.)

Scope and Limitations

The most serious limitations of the Brenner method for synthesizing peptides is the difficulty of removing the salicyloyl group from the peptide.

[289] Wieland, Lang, and Liebsch, *Ann.*, 597, 227 (1955).
[290] Wieland, Bokelmann, Bauer, Lang, and Lau, *Ann.*, 583, 129 (1953).
[291] Brenner, *Angew. Chem.*, 69, 102 (1957).
[292] McConnan and Titherley, *J. Chem. Soc.*, 89, 1318 (1906).
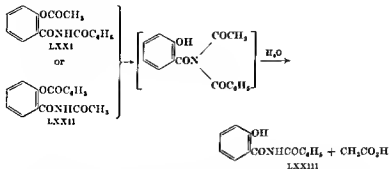
It has been accomplished by treatment with sodium in liquid ammonia, but the yields, presumably low, were not recorded.[293-295]

The reaction appears to be general for O-aminoacylsalicylic acids. The presence of the benzene ring is necessary to bring the reacting groups into spatial proximity so that reaction will occur under mild conditions. The reaction failed with β-hydroxybutyric acid, serine, and cysteine derivatives. However, the use of potassium t-butoxide led to successful rearrangement of derivatives of serine and threonine.[296]

The rearrangement may be repeated to lengthen the peptide chain by one amino acid residue at a time. Optically active methyl salicylglycyl-L-phenylalanylglycinate was prepared in this way.[293, 296, 297]

O-α-Aminoacylsalicylic acids can be employed in place of salicylamides. Thus O-glycylsalicylic acid[296, 298] and O-L-phenylalanylsalicylic acid[296] rearrange in neutral or weakly acid media at room temperature to give the salicylcylamino acid. Since no racemization occurred with L-phenylalanine, it was concluded that an oxazolone was not an intermediate. In contrast to the salicylic acid and amide derivatives, the ester derivatives do not undergo the desired rearrangement. Thus methyl O-glycyl-salicylate does not rearrange to salicylglycine but, instead, gives a diketopiperazine.

If, in place of an O-aminoacylsalicylamide LXXIV the corresponding carbobenzyloxy derivative LXXVI is employed, rearrangement proceeds by way of a nine-membered cyclic acylurea LXXVII. The urea is formed in variable yield by treatment of the carbobenzyloxy derivative LXXVI

[293] Belg 549,274 (to Ciba) (1956)
[294] Brenner, U.S 2,850,491 (to Ciba) [C.A., 53, 5152g (1959)]
[295] Brenner, Can 2nt 578 331 (to Ciba) (1959)
[296] Brenner, Angew Chem, 69, 677 (1957)
[297] Brenner and Zimmermann, Helv Chim Acta, 41, 467 (1958)
[298] Brenner and Zimmermann, Helv Chim Acta, 40, 1933 (1957)
[299] Brenner and Wehrmüller, Helv Chim Acta, 40, 2374 (1957)

with aqueous alkali in the presence of ethyl acetate. The yield would probably be improved if sodium ethoxide were used for the cyclization reaction. The cyclic urea LXXVII reacts with aqueous sodium hydroxide
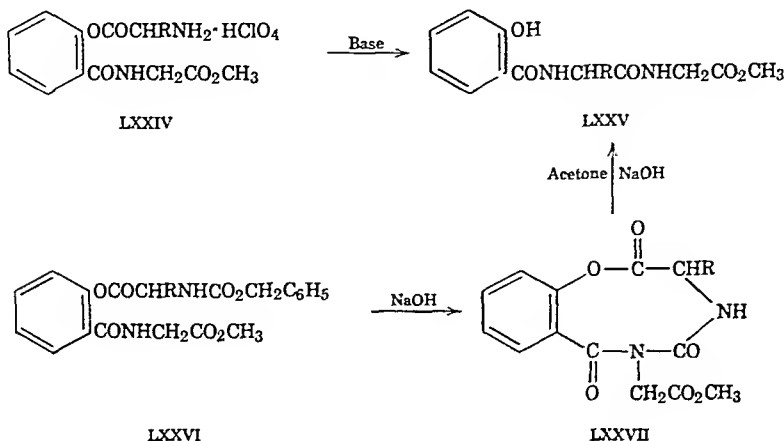
in acetone at room temperature to give the salicyloyl dipeptide ester LXXV. When R is benzyl, the urea LXXVII gives 97% of salicyloyl-DL-phenylalanylglycine methyl ester (LXXV).[293, 294]

Imidazolones become the major product from O-aminoacylsalicyloylamides below pH 8. The tendency toward imidazolone formation decreases with O-aminoacylsalicyloylamino acid esters and is less with O-aminoacylsalicyloyl dipeptides.[288]

Experimental Conditions

The rearrangement of an O-aminoacylsalicyloylamino acid ester LXXIV to the salicyloyl peptide ester LXXV is brought about by bases such as sodium bicarbonate, sodium carbonate, or sodium hydroxide in water, alcohol, or phenol, or by tertiary organic bases such as triethylamine, N-alkylpiperidine, or pyridine preferably in solvents such as chloroform, dioxane, tetrahydrofuran or dimethylformamide. Triethylamine is commonly used and gives satisfactory results in water, methanol, or chloroform.[293, 294] However, triethylamine in tetrahydrofuran leads to the formation of imidazolones as by-products.[288]

The reaction is usually conducted at room temperature for 1 to 14 hours. The reaction mixture is then evaporated to dryness in vacuum and the residue partitioned between ethyl acetate and dilute hydrochloric acid. The ethyl acetate layer is washed with dilute aqueous potassium bicarbonate, dried, filtered, and evaporated to give the salicyloyl dipeptide ester.

The free peptide may be obtained from the salicyloyl peptide in unstated yields by treatment with sodium in liquid ammonia. Thus salicyloyl-glycyl-DL-phenylalanylglycine gave glycyl-DL-phenylalanylglycine, and DL-phenylalanylglycine was obtained from its salicyloyl derivative.[293, 294]

The requisite starting materials are prepared by converting salicylic acid hydrazide to the azide, coupling with an amino acid, and esterifying with methanol and hydrogen chloride to give the salicylylamino acid ester. This product is then acylated on oxygen with a carbobenzyloxy-amino acid chloride.[293] Use of a carbobenzyloxyaminoacyl alkyl carbonate results in a competing reaction between the phenolic hydroxyl and the alcoholic hydroxyl derived from the mixed carbonate. This side reaction is not entirely suppressed by the addition of excess tertiary base. The mixed anhydride derived from phosgene and a carbobenzyloxyamino acid proved satisfactory for acylation of the phenolic hydroxyl at $-70°$,[53] and dicyclohexylcarbodiimide was used to couple carbobenzyloxy-phenylalanine with salicylic acid amide in 85% yield.[218] The optical configuration was not specified.

The removal of the carbobenzyloxy group has been accomplished by hydrogenolysis with a palladium catalyst. Phosphonium iodide has been used to decarbobenzyloxate thiosalicylic acid derivatives.[293] In both cases anhydrous hydrogen bromide in acetic acid should be equally satisfactory.[86]

CYANOMETHYL ESTERS

In addition to phenolic esters, others commonly referred to as activated esters have been used in peptide synthesis. Of these, the cyanomethyl esters are by far the most useful.

The reactions involved in the preparation of an activated ester and its use in the formation of a dipeptide are illustrated below for the cyanomethyl ester of an α-acylamino acid.

$$R_1CONHCHR_2CO_2H + (C_2H_5)_3N + ClCH_2CN \rightarrow$$
$$R_1CONHCHR_2CO_2CH_2CN + (C_2H_5)_3NHCl$$

$$R_1CONHCHR_2CO_2CH_2CN + H_2NCHR_3CO_2C_2H_5 \rightarrow$$
$$R_1CONHCHR_2CONHCHR_3CO_2C_2H_5 + HOCH_2CN$$
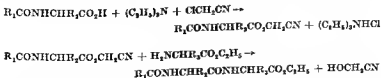
Curtius prepared carboxymethyl hippurate in 1888,[309] but the first use of activated esters in peptide synthesis was described in a series of papers beginning in 1954 by Schwyzer, Iselin, Feurer, and co-workers.

[309] Curtius, J. prakt. Chem. [2] 38, 428 (1888).

Mechanism

Since aminolysis or basic hydrolysis of esters involves nucleophilic attack by an amino or hydroxyl group at the carbonyl carbon atom, factors which tend to make this carbon atom more positive will favor such attack.

The synthesis of penicillin initiated research in this area, and seven classes of activated esters of the type RCO_2CH_2X where X is acyl, carbamyl, acyloxy, carbalkoxy, cyano, alkoxy, or acyloxy were described.[301] These esters were studied because of their ease of hydrolysis but were not used for aminolysis. The presence of X favors nucleophilic

$$R—\overset{\overset{\text{O}}{\|}}{C}_{\delta+}—OCH_2X_{\delta-}$$
$$\uparrow$$
$$^-OH \text{ (or } :NH_2R)$$
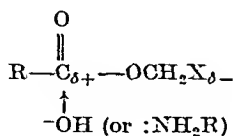
attack and helps to stabilize the anion $\overset{\ominus}{O}CH_2X$ which is formed in the reaction.[302]

Studies of the rate of ammonolysis of methyl phenylacetate led to the conclusion that two reactions occurred, an uncatalyzed reaction of ester and ammonia and a base-catalyzed reaction of ester with amide ion.[303] These results suggested that the addition of a strong base to the activated ester and amine would catalyze the formation of the amide bond by increasing the concentration of amide ions.[304] This supposition was con-

$$RNH_2 + (C_2H_5)_3N \rightleftharpoons R\overset{\ominus}{N}H + (C_2H_5)_3\overset{\oplus}{N}H$$
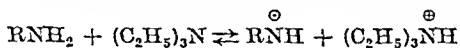
firmed when triethylamine was used to catalyze the reaction between cyanomethyl hippurate and aniline, a relatively weak base; the yield of amide was improved. Triethylamine was without effect when diethylamine, a much stronger base, was substituted for aniline. Sodium methoxide resulted in trans-esterification.

Addition reactions to a carbonyl group may also be acid catalyzed, since the proton on oxygen increases the positive charge on the carbon atom.[305]

$$RC{=}O \; + H^+ \rightleftharpoons RC{=}\overset{\oplus}{O}H \rightleftharpoons R\overset{\oplus}{C}OH$$
$$\underset{OCH_2CN}{|} \qquad\qquad \underset{OCH_2CN}{|} \qquad \underset{OCH_2CN}{|}$$
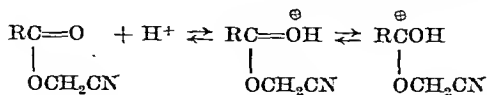
[301] McDuffie, Camillus, and Cooper, U.S. pat. 2,578,570 (to Bristol Laboratories) [*C.A.*, **46**, 7127d (1952)].

[302] Schwyzer, Iselin, and Feurer, *Helv. Chim. Acta*, **38**, 69 (1955).

[303] Betts and Hammett, *J. Am. Chem. Soc.*, **59**, 1568 (1937).

[304] Schwyzer, Feurer, and Iselin, *Helv. Chim. Acta*, **38**, 83 (1955).

[305] Alexander, *Principles of Ionic Organic Reactions*, p. 156, John Wiley & Sons, New York, 1950.

Acetic acid catalyzes the reaction between amines and activated esters,[304] and acetic acid was employed as a catalyst in much of the later work on the synthesis of peptide intermediates.

Cyanomethyl hippurate is hydrolyzed 6.8 times as fast as the methyl ester but is aminolyzed by benzylamine 740 times as fast.[305]

Scope and Limitations

Nature of the Ester. The most reactive esters studied are those derived from chloroacetonitrile or bromomalonic ester. The difference in reaction rate between a methyl ester and a cyanomethyl ester is considerable: methyl hippurate reacts with benzylamine to give only a 1% yield of amide after 11 days, but under the same conditions the cyanomethyl ester gives an 82% yield in half an hour.[305]

The cyanomethyl ester was preferred to all others investigated.[307,308] Amide formation was slower with carbobenzyloxyamino acid esters derived from methyl or ethyl chloroacetate or p-nitrobenzyl chloride. The carboxymethyl ester gave good results at high concentrations of reactants, but was less satisfactory than the cyanomethyl ester in more dilute solutions.[302] The preparation of the dicarbethoxymethyl ester was unsatisfactory because of the formation of ethyltetetracarboxylic ester as a major by-product. The methoxymethyl ester could be prepared only in poor yield, and the methoxymethyl alcohol liberated during aminolysis reacted quantitatively with one equivalent of the amine. The relatively poor results observed in the reaction of the acetonyl ester with amines was probably due to some Schiff base formation. The p-nitrobenzyl ester reacted rather slowly with benzylamine, and a satisfactory yield of amide (65%) could be obtained only by heating the reaction mixture for 2 hours at 77°. β-Diethylaminoethyl hippurate methobromide was rapidly aminolyzed, but the ester is difficult to prepare.[302] Tetrahydropyranyl esters were less active than cyanomethyl esters and tended to decompose on standing. Moreover, an additional asymmetric center is created upon the formation of a tetrahydropyranyl ester. Reaction of the tetrahydropyranyl ester with an amine liberates a mole of 5-hydroxypentanal, which combines with one equivalent of amine.

Propargylphthalylglycinate has been condensed with ethyl glycinate.[310]

Nature of the Amine. The reaction of the activated ester with an amine to form an amide is dependent not only upon the nature of the

[304] Jaehn, Feurer, Hörkmann, and Schwyzer, Chimuu (Sturz), 8, 284 (1954)
[305] Schwyzer, Iselin, and Feurer, Angew. Chem., 65, 747 (1954)
[306] Iselin and Schwyzer, Helv. Chim. Acta, 39, 57 (1956)
[310] Bodánszky, Chem. & Ind. (London), 1957, 624.

ester, including the component acylamino acid, but also upon the nature of the amine. Primary aliphatic amines react with cyanomethyl esters at room temperature, aromatic primary amines require a higher temperature, and secondary aliphatic amines react with difficulty.[301, 307] Although the yields are generally quite good, the reaction may be slow with the more complex amines. Glycine cyanomethyl ester reacts with amino acid esters in 1 to 5 hours,[307] whereas some amino and peptide cyanomethyl esters are allowed to react for 4 days.[311] In the synthesis of peptides the amine component was usually an ester of glycine, leucine, isoleucine, or tyrosine[211, 304] and yields were generally 70%. Where the amine component was a peptide ester, yields of 43% to 96% were obtained.[311]

The amine function may be part of the same peptide bearing the cyanomethyl group, thus permitting the synthesis of cyclic peptides. Trityldiglycylglycine was converted to the cyanomethyl ester in 84% yield. After detritylation with hydrogen chloride the cyanomethyl ester of triglycine hydrochloride was dissolved in dimethylformamide and the solution added during a period of 5 hours to pyridine at 95° to give 36% of cyclohexaglycyl. Under similar conditions the cyanomethyl ester of tetraglycine gave 12.5% of cyclotetraglycyl.[312, 313] The cyanomethyl ester of glycyl-DL-phenylalanylglycine was converted to cyclo-glycylglycyl-DL-phenylalanylglycylglycyl-DL-phenylalanyl in 20% yield.[149]

The removal of a carbobenzyloxy group from carbobenzyloxylated tripeptide cyanomethyl esters with hydrogen bromide in glacial acetic acid, without the expected conversion of the nitrile to an amide,[315] has been reported.[314]

Nature of the α-Acylamino Acid. Limited data are available concerning the α-acylamino acids. Cyanomethyl carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosinate (in which the phenolic group on the tyrosine residue was not protected) reacted with ethyl L-isoleucinate to give 58% of the acylated peptide.[306, 311] Even more noteworthy is the coupling of cyanomethyl tosyl-L-glutaminate with ethyl glycinate in 90% yield;[301] in a patent application the same reaction is reported to give a 72% yield based on the cyanomethyl ester or a 49% yield based on tosyl-L-glutamine.[316] Cyanomethyl phthaloylglycinate is noticeably less reactive than cyanomethyl carbobenzyloxyglycinate.[317]

[311] Iselin, Feurer, and Schwyzer, *Helv. Chim. Acta*, **38**, 1508 (1955).

[312] Schwyzer, Iselin, Rittel, and Sieber, *Helv. Chim. Acta*, **39**, 872 (1956).

[313] Schwyzer, Iselin, Rittel, and Sieber, *Chimia (Switz.)*, **10**, 97 (1956).

[314] Morozova and Zhenodarova, *Zhur. Obshchel Khim.*, **28**, 1661 (1958) [*C.A.*, **53**, 1169f (1959)].

[315] Kerr and Niemann, *J. Org. Chem.*, **23**, 304 (1958).

[316] Australian pat. appl. 6639/55 (to Ciba).

[317] Helferich, Schellenberg, and Ullrich, *Chem. Ber.*, **90**, 709 (1957).

Racemization. Cyanomethyl carbobenzoxy-L-leucinate was coupled with ethyl glycinate, and the product decarbobenzoxylated to give ethyl L-leucylglycinate. This, in turn, was coupled with cyanomethyl hippurate to give ethyl hippuryl-L-leucylglycinate. After hydrolysis the leucine was isolated as its naphthalene β-sulfonate with no evidence of racemization [318] No racemization, however, should have been expected in this reaction

Carbobenzoxy-S-benzyl-L-cysteine, triethylamine, and chloroacetonitrile at room temperature gave 82% of the optically active ester. However, at higher temperatures partial or complete racemization was noticed.[311] Since the optically active esters show no tendency to racemize on recrystallization, it was concluded that the reaction temperature was responsible for the racemization

Experimental Conditions

The cyanomethyl esters have a distinct superiority over other activated esters for peptide synthesis

Preparation of the Ester. The salt is prepared *in situ* by the addition of triethylamine to a solution of the α-acylamino acid and then allowed to react with a halide such as chloroacetone, ethyl chloroacetate, chloroacetonitrile, phenacyl bromide, or *p*-nitrobenzyl bromide,[319] to give the ester

$$RCO_2H + (C_2H_5)_3N + ClCH_2COCH_3 \rightarrow RCO_2CH_2COCH_3 + (C_2H_5)_3NHCl$$
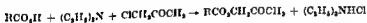
Trifluoroethoxy trifluoroacetylglycinate, prepared from trifluoro-acetylglycyl chloride and 2,2,2-trifluoroethoxymagnesium iodide, reacted with ethyl glycinate to give 94% of the ethyl trifluoroacetylglycylglycinate.[320]

Cyanomethyl carbobenzoxyglycinate has been prepared by two methods [321] In the first, carbobenzoxyglycine was heated under reflux in ethyl acetate with one equivalent of triethylamine and a 50% excess of chloroacetonitrile for 3 hours to give 83% of the ester Cyanomethyl hippurate was prepared in other solvents in a similar fashion, the yield was 80% in ethyl acetate, 83% in acetone, 80% in benzene, 70% in acetonitrile, and 75% in dimethylformamide.[318] The second method consisted in covering the carbobenzoxyglycine with a 50% excess of triethylamine and three equivalents of chloroacetonitrile. After the initial exothermic reaction had subsided, the mixture was heated at 70°

[318] Schwyzer and Isehn. *Ann Acad Sci Fennicae, Ser A. II*, No 60, 181 (1955) [*C A ,*
50, 5526c (1956)]
[319] Lyman and Reid, *J Am. Chem Soc* , **39**, 701 (1917)
[320] Weygand and Swoboda, *Chem Ber* , **39**, 639 [1957]
[321] Schwyzer, Feurer, Iselin, and Kägi, *Helv Chim. Acta*, **38**, 83 (1955)

for $\frac{1}{2}$ hour. This procedure gave a 94% yield.[321] The ester was isolated by removing the solvent in vacuum, taking up the residue in ethyl acetate, and washing the solution with dilute hydrochloric acid, aqueous sodium bicarbonate, and water. Removal of the solvent left the ester, which is readily recrystallized.

In general, the cyanomethyl esters of α-acylamino acids may be prepared in yields of 60–95% under mild conditions, and the removal of by-products is a simple matter. Solid cyanomethyl esters usually crystallize well;[307, 308, 316] the liquid esters are distillable.[302, 316, 321] The esters can be stored until needed.[308]

The reaction of 2-phenyl-4-bromo-5-oxazolone with ethyl glycolate gave (after treatment with water to replace bromine by hydroxyl) the carbethoxymethyl ester of α-hydroxyhippuric acid. The activated ester reacted with ethyl glycinate and with ethyl phenylalaninate to form the peptide derivatives.[322]

Formation of the Amide Bond. The best solvent for amide bond formation is absolute ethyl acetate. Hydroxylated solvents give low yields, and the reaction is relatively slow in benzene, chloroform, dioxane, and acetonitrile. Ethylene glycol, which normally catalyzes the aminolysis of an ester, decreases the aminolysis rate of cyanomethyl hippurate.[302] Under otherwise identical conditions, N-benzylhippurylamide was prepared from cyanomethyl hippurate in 82% yield in ethyl acetate, 60% yield in methanol, 56% yield in 1:1 ethanol-water, and 74% yield in 2:3 dimethylformamide-water.[316]

Better results are obtained when concentrated solutions are used for peptide bond formation.[302] For example, cyanomethyl hippurate reacted with an equivalent amount of benzylamine in ethyl acetate in $\frac{1}{2}$ hour at room temperature to give 82% of amide when the cyanomethyl ester was present in a concentration of 0.5 mole per liter, and only 51% when the concentration was 0.1 mole per liter. The use of a 100% excess of benzylamine increased the yield to 96% (calculation based on the ester).[316] The peptide bond has also been formed by heating an N-trifluoroacetyl-amino acid with the ester of an amino acid without a solvent, but experimental details are lacking.[323]

The by-product cyanomethanol has not been observed to react with the amine component.

Yields are improved by carrying out the reaction in the presence of 5–10 mole per cent of acetic acid as a catalyst.[306]

A reaction time of 4 days at room temperature has been commonly

[321] Shemyakin, Ravdel, and Chaman, *Doklady Akad. Nauk S.S.S.R.*, **107**, 706 (1956) [*C.A.*, **50**, 14028f (1956)]. Cf. *C.A.*, **51**, 3452a (1957).
[323] Weygand, Geiger, and Swodenk, *Angew. Chem.*, **68**, 307 (1956).

used for peptide synthesis,[311] although a glycine ester may be acylated in a few hours.[324] Amino acid esters with bulky side chains require longer time for acylation.[364]

Experimental Procedures

Cyanomethyl Hippurate.[318] To 3.58 g. of hippuric acid (0.02 mole) and 3.03 g. of triethylamine (0.03 mole) in 30 ml. of ethyl acetate was added 2.27 g. of chloroacetonitrile (0.03 mole) and the mixture was heated under reflux for 3 hours. It was then cooled, freed from the solid triethylamine hydrochloride, and the ethyl acetate solution washed with dilute aqueous sodium bicarbonate and water, dried, and evaporated. The residue crystallized on addition of ethyl ether to give 3.47 g. (80%) of hippuric acid cyanomethyl ester, m.p. 97–99°. Recrystallization from acetone-ether raised the melting point to 99–100°.

p-Nitrobenzyl Hippurate.[310] The method is analogous to that described above except that p-nitrobenzyl chloride is used in place of chloroacetonitrile and heating is continued for 15 hours. The ester, m.p. 134–135°, after recrystallization from ethanol, was obtained in 82% yield.

Cyanomethyl Carbobenzyloxyglycyl-DL-alanylglycinate.[318] A solution of 0.44 g. of carbobenzyloxyglycyl-DL-alanylglycine and 0.2 g. of triethylamine in 1 ml. of chloroacetonitrile was heated for ¾ hour at 80°. The solvent was removed under reduced pressure, the residue taken up in ethyl acetate, and the solution washed with aqueous sodium bicarbonate and water. The dried solution was evaporated to give 490 mg. of crystalline ester. Recrystallization from acetone gave colorless crystals of product, m.p. 145–145.5°. The yield was 470 mg. (95%).

Ethyl Trifluoroacetylglycylglycylglycinate.[320] A solution of 1.60 g. of cyanomethyl trifluoroacetylglycylglycylglycinate and 0.742 g. of ethyl glycinate in 5 ml. of ethyl acetate was heated at 110° for 90 minutes, evaporated in a high vacuum, and the residue sublimed at a bath temperature of 180–190° to give 1.71 g. (91%) of product, m.p. 234–234°.

Ethyl (N-Carbobenzyloxy-S-benzyl-L-cysteinyl)-O-tetrahydropyranyl-L-tyrosyl-L-isoleucinate.[321] To a solution of 5.76 g. (0.015 mole) of cyanomethyl N-carbobenzyloxy-S-benzyl-L-cysteinate and 5.80 g. (ca. 0.014 mole) of crude O-tetrahydropyranyl-L-tyrosyl-L-isoleucine ethyl ester in 6.5 ml. of dry ethyl acetate was added 30 mg. of acetic acid as a catalyst. The product gradually separated as a gelatinous precipitate. The reaction mixture was allowed to stand for 4 days at room temperature, then triturated with ethyl ether and filtered to give

³⁶⁴ Iselin, Feurer, and Schwyzer, *Chimia (Switz.)*, **8**, 264 (1954).

8.9 g. of product, m.p. about 90°. Two recrystallizations from acetone-ether gave 6.73 g. (65% based on the tetrahydropyranyl ester) of fine needles, m.p. 143–145°, $[\alpha]_D^{23}$ $-46° \pm 1°$ ($c = 3.92\%$ in CHCl$_3$). Further recrystallization from methanol or ethanol did not change the melting point.

ACYLIMIDAZOLES

The ammono anhydride resulting from the replacement of one carbonyl oxygen atom and the central oxygen atom of an anhydride with nitrogen
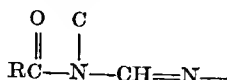
will react with amines at the carbonyl carbon atom to form amides. Thus benzoyl-L-histidine methyl ester (LXXVIII) reacts with hippuryl chloride to give *im*-hippuryl-N-benzoyl-L-histidine methyl ester* (LXXIX), which in turn reacts with sodium glycinate to give benzoyl-glycylglycine (LXXX) in 35% yield.[325]

$$C_6H_5CONHCH_2CONHCH_2CO_2H + LXXVIII$$
$$LXXX$$
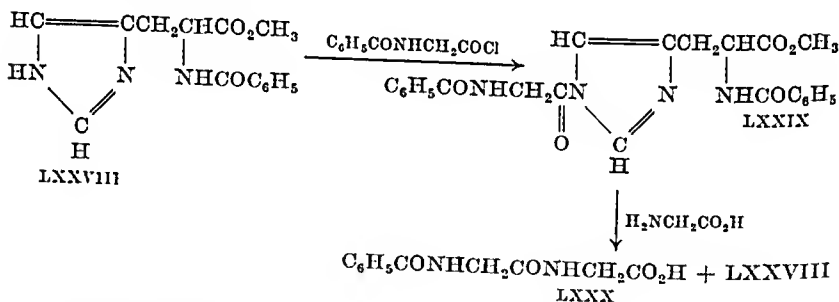
The ready cleavage of the imidazole ring under Schotten-Baumann reaction conditions has been known for a long time.[326] Thus the reaction
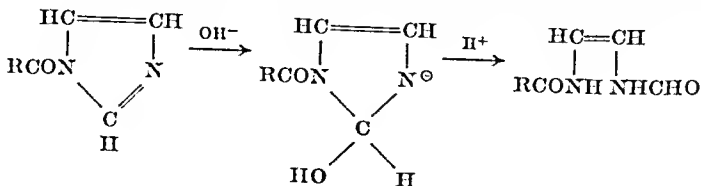
of benzoyl-L-histidine methyl ester (LXXVIII) with benzoyl chloride in

---

* The prefix "*im*" is used to indicate substitution on the imidazole ring. See ref. 229.
[325] Bergmann and Zervas, *Z. physiol. Chem., Hoppe-Seyler's*, **175**, 145 (1928).
[326] Bamberger and Berlé, *Ann.*, **273**, 351 (1892).

carbon dioxide evolution ceases, the amino acid ester is added. The reaction is allowed to proceed at least 15 minutes before the solution is concentrated and the product purified by washing with acid and aqueous sodium bicarbonate.

The acylation of ethyl glycinate with carbobenzyloxyglycyl-L-phenyl-alanylimidazole in tetrahydrofuran at room temperature led to a product containing approximately 5% of the DL form. At −10° in dimethyl-formamide, however, racemization amounted to less than 0.5% and the L form, m.p. 119.8–120.3°, $[\alpha]_D^{25}$ −12.2° ± 1.25 ($c = 2\%$, ethanol), was obtained in 87% yield.

ACYLPYRAZOLES

A preliminary study[332] shows that α-acylamino acid hydrazides react with acetylacetone to give acylaminoacylpyrazoles which will, in turn, acylate an amino acid ester.

$$p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCH}_2\text{CONHNH}_2 + \text{CH}_3\text{COCH}_2\text{COCH}_3 \rightarrow$$

$$p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCH}_2\text{C}\underset{\underset{\text{O}}{\|}}{\text{N}}\begin{array}{c} \text{N}{=}\text{CCH}_3 \\ \diagup \quad\quad | \\ \text{C}{=}\text{CH} \\ | \\ \text{CH}_3 \end{array}$$

LXXXIV

$$\text{LXXXIV} + \text{H}_2\text{NCH(CH}_3)\text{CO}_2\text{C}_2\text{H}_5 \rightarrow$$

$$p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCH}_2\text{CONHCH(CH}_3)\text{CO}_2\text{C}_2\text{H}_5 + \text{HN}\begin{array}{c} \text{N}{=}\text{CCH}_3 \\ \diagup \quad\quad | \\ \text{C}{=}\text{CH} \\ | \\ \text{CH}_3 \end{array}$$
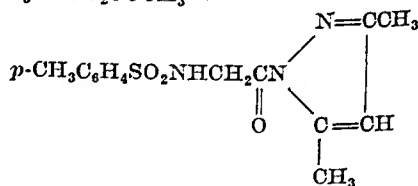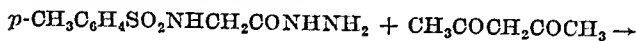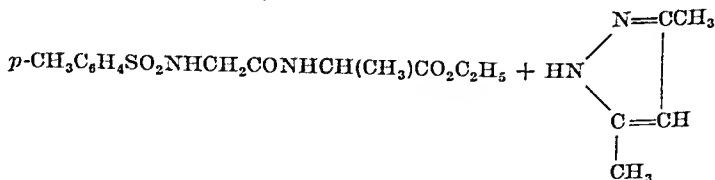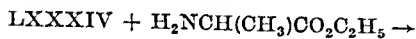
The acylpyrazoles were prepared by heating the α-tosylamino acid hydrazides with excess acetylacetone; a 10–20% excess in ethanol was used with glycine and alanine, a 100% excess and no solvent with valine. Yields, of α-tosylaminoacylpyrazole were 80, 60, and 51%, respectively.

The general procedure for the formation of the peptide bond is illustrated by the following example.

Ethyl p-Toluenesulfonylglycyl-DL-alaninate. A mixture of 6.1 g. (0.02 mole) of N-p-toluenesulfonylglycyl-3,5-dimethylpyrazole and 2.7 g. (0.023 mole) of ethyl DL-alaninate was heated for 1 hour on a steam bath to give an oil. Unreacted ethyl alaninate, b.p. 48°/11 mm., was removed

[332] Ried and Schleimer, Ann., 619, 43 (1958).

in vacuum, and 3,5-dimethylpyrazole removed by steam distillation. The residual oil was taken up in ether, concentrated, and triturated with water to give a crystalline precipitate which was recrystallized from aqueous ethanol to give 80.5% of product, m p 57°.

The latter product was converted to the hydrazide and then to the 3,5-dimethylpyrazole in 70% yield. Reaction of the resulting 1-(N-p-toluenesulfonylglycyl-DL-alanyl)-3,5-dimethylpyrazole with ethyl DL-valinate gave a 56% yield of the tosyl tripeptide ester.

α-ACYLAMINO THIOL ESTERS AND THIOL ACIDS

Introduction

Acetyl coenzyme A, the source of biologically active acetyl groups, is a thiol ester having a CH_2COS grouping.[333] Thiol esters of α-acylamino acids are not only of preparative value but also of biochemical interest.

The synthesis of thiol esters usually involves reaction of an α-acylamino acid mixed anhydride with a mercaptan or thiophenol. The same mixed anhydride LXXXV may be produced by reaction of the α-acylamino acid R.SH:

(a) $R_1CONHCHR_2COOCOC_2H_5 + HSR_3 \rightarrow$
$$R_1CONHCHR_2COSR_3 + C_2H_5OH + CO_2$$
$$\text{LXXXV}$$

(b) $R_1CONHCHR_2COSR_3 + H_2NR_4 \rightarrow R_1CONHCHR_2CONHR_4 + HSR_3$
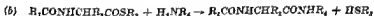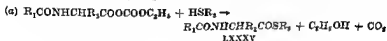
with a mixed anhydride of the thiol R_3SH. This procedure was used in the synthesis of a cyclic peptide.[334] sodium p-nitrothiophenolate and phosphorus trichloride gave a 55% yield of tri p-nitrothiophenyl phosphite LXXXVI.[28],[335] This product with carbobenzyloxyglycyl-L-

$$PCl_3 + 3NaSC_6H_4NO_2\text{-}p \rightarrow P(SC_6H_4NO_2\text{-}p)_3 + 3NaCl$$
$$\text{LXXXVI}$$
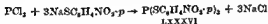
leucylglycyl-L-leucylglycine afforded the corresponding carbobenzyloxy pentapeptide p-nitrothiophenyl ester (LXXXVII) in 98% yield. Removal

$$\text{Cbzo.Gly.L Leu.Gly.L Leu Gly.OH} + \text{LXXXVI} \rightarrow \text{—GlySC}_6\text{H}_4\text{NO}_2 p$$
$$\text{LXXXVII}$$

$$\downarrow \text{HBr to CH}_3\text{CO}_2\text{H}$$

$$\text{COSC}_6\text{H}_4\text{NO}_2\text{-}p$$
$$\text{NH}_3{}^+, \text{Br}^-$$

$$\xrightarrow{\text{MeO}}$$
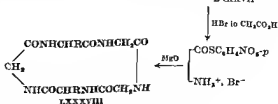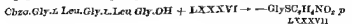
333 Lynen and Reichert, *Angew Chem*, **63**, 47 (1951).
334 Kenner and Turner, *Chem & Ind (London)*, **1955**, 602
335 Farrington, Kenner, and Turner, *Chem & Ind (London)*, **1955**, 601.

of the carbobenzyloxy group followed by liberation of the free base allowed amide bond formation to take place with the production of a cyclic pentapeptide formulated as LXXXVIII. Since doubling normally occurs in the cyclization of peptides with an odd number of amino acids,[146-149] a cyclodecapeptide might have been expected. The use of tri-*p*-nitrothiophenyl phosphite (LXXXVI) subjects the acylamino acid or peptide to one anhydride-forming step rather than two.

The thiol esters are relatively stable toward hot water and dilute acid but are slowly attacked by base.[336] Aminolysis generally occurs readily, but the rate depends upon a number of factors discussed more fully below.

Thiol esters possess certain advantages over most other mixed anhydrides as a result of their stability toward weak bases, anhydrous acids, and heat. The coupling of an α-acylamino acid thiol ester with the sodium salt of an amino acid will lead usually to a pure dipeptide derivative.[336] For example, in the coupling of carbobenzyloxyglycine thiophenyl ester with phenylalanine in basic solution to give carbobenzyloxyglycyl-phenylalanine and thiophenol, extraction of the reaction mixture with ether will remove unreacted carbobenzyloxyglycine thiophenyl ester and thiophenol. Acidification then precipitates only the product. With most other mixed anhydrides, acidification would precipitate unreacted carbobenzyloxyglycine with the product.

A further advantage of thiol esters is that a carbobenzyloxy, a carbo-*t*-butoxy, or a carbocyclopentyloxy protecting group is readily removed from a peptide thiol ester with anhydrous hydrogen bromide without affecting the thiol ester group. The less convenient phosphonium iodide may also be used for removal of the carbobenzyloxy group from a peptide thiophenyl ester.[337] The resulting intermediates are of interest, both for the preparation of polymers in which two or more amino acids are repeated in known sequence, and for the preparation of cyclic peptides. Thus triglycylthioglycolic ester in dimethylformamide was added to pyridine at 60° over a 10-hour period to give a 69% yield of cyclohexaglycyl.[312]

α-Amino acid thiophenyl esters have been coupled with acyldipeptides in good yield via the mixed carbonic anhydride. This lengthens the peptide chain and forms an acyltripeptide thiophenyl ester ready to undergo further coupling. Alternatively, the thiol ester group may be removed by hydrogen peroxide in acetic acid.[15]

The stability of thiol esters is indicated by the fact that initially odorless crystals of the thiophenyl esters of carbobenzyloxyglycine and carbo-benzyloxytryptophan developed only a slight odor after 1 year.[224]

The pioneering work of Wieland suggested that reaction of mixed anhydrides of α-acylamino acids with hydrogen sulfide would lead to α-acylamino thioacids. Reaction of phthaloylglycine with ethyl chloroformate and then with hydrogen sulfide gave phthaloyl thioglycine in 61% yield.[339] The same product was obtained in good yield from phthaloylglycyl chloride and sodium hydrosulfide Methyl phthaloylglycylglycylglycinate was obtained in unstated yield from phthaloylthioglycinate and methyl glycinate. In similar manner thiolhippuric acid and phthaloylthiolglycine were prepared as were thiolacetic acid, thiolbenzoic acid, and p-phenylthiolbenzoic acid.[340] The mixed anhydride of carbobenzyloxyglycine and isobutyl carbonate was converted to the thiol acid and the thiol acid converted to the amide in 24% over-all yield [15] The α-acylaminothiol acids generally offer no advantage in peptide synthesis over the thiol esters and indeed require an additional step

Mechanism

The reaction between thiol esters and amines is considered to be a bimolecular nucleophilic substitution.[341,342]

The weak permanent polarization of the C—S bond in the thiol ester is supplemented by the larger polarization induced by the approach of the amine. Sufficiently close approach of the amine leads to the transition state A and to the amide and thiol

$$R_1NH_2 + \underset{\underset{R_2}{|}}{\overset{\overset{O}{\|}}{C}} - SR_3 \rightleftarrows \left[\underset{\underset{R_2}{|}}{\overset{\overset{O}{\|}}{R_1 N_{\delta+}^{\overset{H}{|}} C} - SR_3} \right] \rightleftarrows \left[\underset{\underset{R_2}{|}}{\underset{A}{\overset{\overset{H_{\delta+}}{|}}{R_1 N} \cdot \overset{\overset{O}{\|}}{C} - SR_3^{\delta-}}} \right]$$

$$\rightleftarrows$$

$$R_1 N \underset{\underset{R_2}{|}}{\overset{\overset{O}{\|}}{-C}} + HSR_3$$
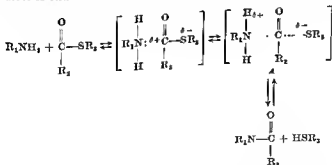
This mechanism suggests that changes in R_3 which will increase the polarization of the C—S bond will favor amide bond formation This

[339] Sheehan and Johnson, J Am Chem Soc, 74, 4726 (1952).
[340] Cronyn and Jiu, J Am Chem Soc, 74, 4726 (1952).
[341] Schwyzer and Hürlimann, Helv Chim Acta, 37, 155 (1954).
[342] Schwyzer, Helv Chim Acta, 36, 414 (1953).

has been verified. For example, *p*-nitrothiophenyl carbobenzyloxy-glycinate reacted with alanine in aqueous dioxan 140 times as fast as the thiophenyl ester.[335] The carbobenzyloxy thiol esters of acylamino acids[343] are especially useful for peptide syntheses.[341]

The maximum yields of anilide obtained in the reaction of various thiol esters of acetic, benzoic, and hippuric acid with aniline in 1% aqueous solution were in the order: $-SC_2H_5 \ll -SC_6H_5 \ll -SCH_2CH_2NHCOCH_3 \ll -SCH_2CH(NHCOCH_3)CO_2H < -SCH_2CH_2CO_2H < -SCH_2CO_2H$.

Another method of increasing the C—S bond polarization would be to form a bond between an electrophilic reagent, E, and the sulfur through the $3p$ electrons of the latter. The catalysis by aminoacylase of the

$$R_1CO-S-R_2 + E \rightarrow R_1\overset{\delta+}{C}O-\underset{\underset{E^{\delta-}}{|}}{S}-R_2$$
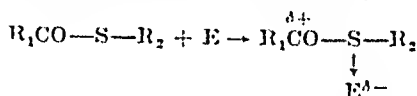
reaction between benzoyl coenzyme A and glycine to give hippuric acid may be an instance of this type of polarization.[341]

A more practical application to peptide synthesis is the use of metal ions as the electrophilic reagent E. Catalysis by silver ion is explained on the basis of a complex of the thiol ester, silver ion, and amine.
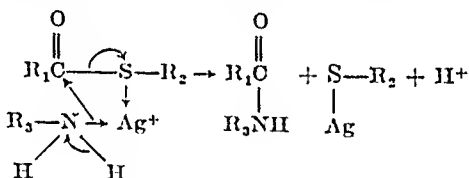
The varying degrees of effectiveness of different metal ions may be due to the difference in their ability to coordinate with the amine.[341]

In the reaction between hippuryl thioglycolic acid and glycine with lead acetate as catalyst, the lead salt of hippurylthioglycolic acid was isolated as an intermediate. The structure LXXXIX was proposed for this intermediate to explain the catalytic effects of the lead ion.

LXXXIX
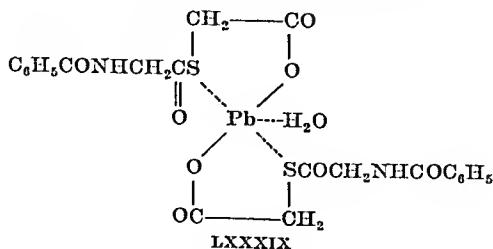
[343] Fr. pat. 1,090,837 (to Ciba) [*Chem. Zentr.*, **129**, 2874 (1058)].
[344] Fr. pat. 1,090,838 (to Ciba) [*Chem. Zentr.*, **129**, 853 (1058)].

Aqueous bicarbonate will catalyze the cleavage (either hydrolysis or aminolysis) of α-aminoacyl thiols, but the ions HPO_4^{-2}, SO_4^{-2}, HSO_3^-, and HCO_3^- do not.[315] *The initial step may involve reaction of the amine and carbon dioxide or bicarbonate ion with the loss of a proton.*

$$RNH_2 + CO_2 \rightleftharpoons [R\overset{+}{N}H_2 - \overset{O}{C}O_2^-] \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} RNHCO_2^-$$

The acetamidoethyl ester XC (R = CH_3CONH-) was aminolyzed or hydrolyzed more rapidly than the ethyl ester (R = H) and the same reactions involving the amide XCI proceeded more rapidly when R = H than when R = CH_3. These results obtained in the presence of aqueous

$$H_3NCH(CH_2)_2COSCH_2CH_2R$$
$$\text{XC}$$

$$H_3NCH(CH_2)_2COSCH_2CH_2NRCOCH_2NH_2$$
$$\text{XCI}$$
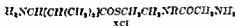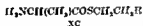
bicarbonate were interpreted as indicating cyclization of the carbonate of XC to XCII, followed by rearrangement to the diacylimide XCIII. *The latter compound can undergo ring opening via aminolysis or hydrolysis at either of the acyl groups.*
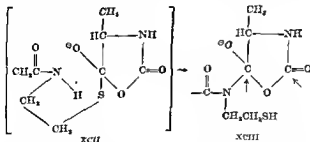
The "bicarbonate effect" has been used to synthesize alanylglycine from thiolalanine and glycine. *Peptide formation did not take place in the absence of aqueous sodium bicarbonate.*[318]

Scope and Limitations

Comparatively few peptides have been prepared from α-acylamino acid thiol esters Acyl derivatives of glycine, phenylalanine,[335,336] β-alanine,[336,337] S-benzyl-L-cysteine,[316] and tryptophan[333] have been used as

³¹⁵ Wieland, Lambert, Lang, and Schramm, *Ann*, **597**, 181 (1955)
³¹⁶ Wieland and Bartmann, *Chem Ber*, **89**, 946 (1956)
³¹⁷ Wieland, U S pat 2,769,164 to Boehringer Sohn [*C A*, **50**, 7848b (1956)].
³¹⁸ Hooper, Rydon, Schofield, and Heaton, *J Chem , Soc* 1956, 3148.

acidic components in peptide synthesis. When the amine component is proline, acylation with carbobenzyloxyglycine thiophenyl ester or carbobenzyloxyglycylglycine thiophenyl ester proceeds in yields of about 80%, whereas with the mixed carbonic anhydrides of the acylated amino acid or dipeptide yields are 20% or less.[59] A series of cyclopolycaprolactams ranging from the cyclodipeptide to the cyclohexapeptide has been prepared.[273]

The common practice of preparing the α-acylamino acid thiol ester from a mixed anhydride of the α-acylamino acid limits the utility of this method because of the extra step. In general, the use of tri-p-nitrothiophenyl phosphite for the synthesis of the α-acylamino thiol esters[335] obviates this disadvantage. Attempts to prepare the p-nitrothiophenyl ester of carbobenzyloxy-L-leucylglycyl-L-leucylglycyl-L-leucylglycyl-L-leucylglycine failed, presumably because of the insolubility of the acylpeptide.[349]

It would be of interest to extend the tri-p-nitrothiophenyl phosphite method to acyl derivatives of the hydroxy amino acids. If it functions satisfactorily, the scope of the acylaminoacyl thiol ester and the activated ester procedure would be similar.

Hydrogen sulfide reacts with amino acid thiophenyl esters to give the aminothiol acid and thiophenol.[350-352] The thiophenyl esters may be prepared from the amino acid chloride hydrochloride and thiophenol. These reactions follow the typical pattern of an anhydride and an acid giving a new anhydride with liberation of the stronger acid as shown in the accompanying equations.

$$HCl \cdot H_2NCH(CH_3)COCl + HSC_6H_5 \rightarrow HCl \cdot H_2NCH(CH_3)COSC_6H_5 + HCl$$

$$H_2NCH(CH_3)COSC_6H_5 + H_2S \rightarrow H_2NCH(CH_3)COSH + C_6H_5SH$$
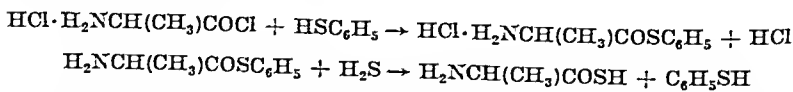
Actually the aminothiol acids were shown to exist as zwitter ions. They failed to acylate ammonia or amino acids.[346,351] If the amino group was further separated from the thiol acid group, reactivity increased; thio-β-alanine, for example, polymerized on heating at 100° for 48 hours.[352]

Treatment of benzylpenicillin with ethyl chloroformate and triethylamine in chloroform followed by reaction with hydrogen sulfide gave the symmetrical benzylpenicillinic thiol anhydride as a crystalline solid.[353] Unlike the oxygen anhydrides which can acylate only 1 mole of amine,

[249] Kenner, Thomson, and Turner, *J. Chem. Soc.*, 1958, 4148.

[250] Wieland and Sieber, *Naturwiss.*, 40, 242, 300 (1953).

[251] Wieland, Sieber, and Bartmann, *Chem. Ber.*, 87, 1093 (1954).

[252] Wieland and Freter, *Chem. Ber.*, 87, 1099 (1954).

[253] Evans and Jansen, *J. Chem. Soc.*, 1954, 4037.

thiol anhydrides can acylate 2 moles. However, benzylpenicillinic thiol
anhydride gave with cyclohexylamine only a 42% yield of benzyl-
penicillin cyclohexylamide. Thiol anhydrides of other acylamino acids
have not been prepared.

The α- and γ-thiophenyl esters of carbobenzyloxyglutamic acid reacted
with ammonia to give homogeneous products.[354] However, the corre-
sponding α- and γ-carbobenzyloxythiolglutamic acids always gave a
mixture of S-α- and S-γ-glutamylglutathione from pure starting materials
The latter result may probably be ascribed to the use of base in the
synthesis rather than to the use of thiol acid in place of a thiophenyl
ester. The interconversion of α and γ isomers of glutamic acid is known
to occur with ease.[87, 88, 104, 105, 355]

Although S-valylcysteamine was prepared by fusion of valyl chloride
and cysteamine hydrochloride,[356] this reaction failed when cysteine was
used in place of cysteamine.[299]

The exchange reaction between thiophenyl esters and hydrogen sulfide
was employed to prepare S-leucyl-, S-valyl-, and S-methonyl-gluta-
thiones,[360] but these thiol esters proved unsatisfactory for peptide syn-
thesis S-Methionylglutathione reacts in aqueous trimethylamine to

$$RCOSC_6H_5 + R'SH \rightleftharpoons RCOSR' + C_6H_5SH$$
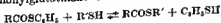
give oligopeptides of methionine as shown by paper chromatography [357]
S-Alanyl- and S-acetylglycyl-glutathione have also been prepared.[357]

The reaction of alanine thiophenyl ester hydrochloride with coenzyme
A gave S-alanyl-coenzyme A hydrochloride, isolated by electrophoresis
When this compound was treated with glutamic acid in a solution buffered
at pH 8, the product was reported to be alanylglutamic acid on the basis
of an electropherogram [358]

Tritylglycylglycine could not be converted to the azide via the hydra-
zide, but it was converted to the thiophenyl or thiobenzyl ester via the
alkyl carbonate mixed anhydride.[9] Acylpenicillamines react with
isobutyl chloroformate and triethylamine to give α-acylamino-β-propio-
thiolactones[359] which have been used for peptide synthesis L-α-
Phthalimido-β-propiothiolactone reacts with L-methionine ethyl ester to
give a 31% yield of crude N-phthaloyl-L-cysteinyl-L-methionine ethyl
ester.[360]

[354] Sachs and Waelsch, J Am Chem Soc. 77, 6600 (1955)
[355] Clayton and Kenner, Chem & Ind (London), 45, 1205 (1953)
[356] Wieland and Bokelmann, Ann 576, 20 (1952)
[357] Strecker, Mela, and Waelsch, J Biol Chem, 212, 223 (1955)
[358] Stewart and Woolley, Nature, 176, 218 (1955)
[359] Kosuyanta, Kildisheva, and Petrova, Bull soad sci URS S S, classe sci chim, 1955,
689, 696 [C A , 50, 7055e, 7056e (1956)]
[360] Fles, Markovac-Prpic, and Tomašic, J Am Chem Soc, 80, 4654 (1958)

Basic German patents have been issued to cover peptide bond formation from amino acids or peptides or their esters and α-acylaminothiol esters NHR(X)CHCOSA, where R is an alkyl, aralkyl, acyl, or other amine-protecting group, X is a residue as found in amino acids and peptides, and A is an alkyl, aryl, aralkyl, or similar residue.[317, 361, 362]

French patents[313, 314] claim the preparation and use of compounds differing from those described in the German patents in the nature of the thiol portion of the molecule. They may be represented as NHR(X)CHCOSYZ, where Y is methylene, ethylene, propylene, or phenylene, and Z represents an electron-acceptor group such as carboxyl, sulfonyl, or nitro. The examples refer to the use of thioglycolic and thiosalicylic acids which should give the most reactive intermediates. Separation of the thiol and electron-accepting group by a propylene chain partially nullifies the advantage of having the electron-accepting group in the molecule. Thioglycolic acid combines the advantages of a thiol ester with those of an activated ester in respect to reactivity.

Patents also claim the use of metal salts such as silver nitrate or lead acetate to increase the yield of amide obtained from thiol esters.[363] In some reactions the catalytic effect is quite marked, as in the reaction of benzoylpantethein with glycine to give an 80% yield of hippuric acid in the presence, but not in the absence, of silver ion.

Racemization

Preliminary results with tri-p-nitrothiophenyl phosphite for peptide synthesis indicate that the intermediates are obtained with higher optical purity than by some other methods of synthesis.[335] Thus the reaction of the lithium salt of carbobenzyloxyglycyl-L-phenylalanine with tri-p-nitrothiophenyl phosphite in dimethylformamide at 18° gave a 99% yield of carbobenzyloxyglycyl-L-phenylalanyl-p-nitrothiophenyl ester with a rotation of −67°. The same thiol ester, prepared from the same lithium salt with sulfur trioxide in dimethylformamide, gave a 67% yield of product with a rotation of −36°. The thiol ester, prepared from the mixed anhydride of ethyl chloroformate and carbobenzyloxyglycyl-L-phenylalanine followed by reaction with p-nitrothiophenol in dimethyl formamide, was optically inactive. Carbobenzyloxyglycyl-L-phenyl-alanine p-nitrothiophenyl ester is reported to give a quantitative yield of carbobenzyloxyglycyl-L-phenylalanylglycine and equally good results in other amide syntheses.[335]

[361] Wieland, Ger. pat. 875,358 (to Boehringer Sohn) [*Chem. Zentr.*, 126, 3734 (1955)].

[362] Brit. pat. 699, 678 (to Boehringer Sohn) [*C.A.*, 49, 2490f (1955)].

[363] Fr. pat. 1,090,839 (to Ciba) [*Chem. Zentr.*, 129, 852 (1958)].

The use of nitrophenyl thiol esters may sometimes result in racemization.[311] The reaction of the thiol ester of carbobenzoxyglycyl-L-alanine with L-phenylalanylglycine gave almost half as much DL isomer as LL isomer.[38] p-Nitrophenyl thiol esters with a terminal glycine residue may help to avoid the substantial risk of racemization.[349]

The α- and γ-thiophenyl esters of α-N-acylglutamic acids have been synthesized from an α-N-acyl-L-glutamic acid anhydride and thiophenol under a variety of experimental conditions.[99, 354] In weakly polar media in the presence of a weak base the optically active α-thiophenyl ester is the major product.[99] The use of triethylamine increases the proportion of the γ-ester (especially in the case of α-N-phthaloyl-L-glutamic acid anhydride) without causing racemization. However, in strongly polar solvents, the use of triethylamine gives almost exclusively the γ-ester with racemization.

Intramolecular Aminoacyl Migration*

An α-aminoacyl group on a sulfur atom will migrate to a nitrogen atom in a sterically favorable position. Thus thiophenyl valinate (XCIV) and cysteine give S-valylcysteine (XCV), which rearranges rapidly to N-valylcysteine (XCVI). The reaction was allowed to proceed for two

$$H_2NCHCOSC_6H_5 + HSCH_2CH(NH_2)CO_2H \rightarrow H_2NCHCOSCH_2CH(NH_2)CO_2H$$
$$CH(CH_3)_2 \qquad\qquad\qquad\qquad\qquad CH(CH_3)_2$$
$$XCIV \qquad\qquad\qquad\qquad\qquad\qquad\qquad XCV$$

$$HSCH_2CHCO_2H$$
$$H_2NCHCONH$$
$$CH(CH_3)_2$$
$$XCVI$$
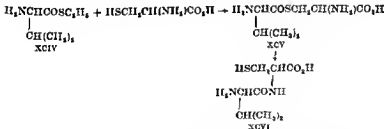
minutes at pH 7.5, stopped by the addition of acid, and the final product was identified by chromatography. Under the same conditions, substitution of glycine for cysteine gave only a trace of valylglycine, and other aliphatic amino acids gave no valyl peptides, suggesting that the reaction occurs first at the thiol group. Histidine gave valylhistidine, an indication that the initial reaction was probably at the ring nitrogen.

Somewhat unexpected was the further observation that thiophenyl esters will acylate a neighboring amide group.[290] S-Valyl-N glycylcysteamine (XCVII) dihydrochloride was treated with base and the

_____

* The optical configurations of the amino acids used in the migration studies, while not specified, were presumably L.

product chromatographed. Since N-valylglycylcysteamine (*A*) and N-glycylvalylcysteamine (*B*) could not be separated from each other by this means, the mixture was treated with S-methyl isothiourea and hydrolyzed. The presence of small amounts of α-guanidoacetic acid together with large amounts of α-guanidoisovaleric acid showed that some of the glycine was in the terminal position. This led to the deduction that a bis(aminoacyl) imide *C*, a new form of mixed anhydride, may have been the intermediate. The postulated reactions are shown below.
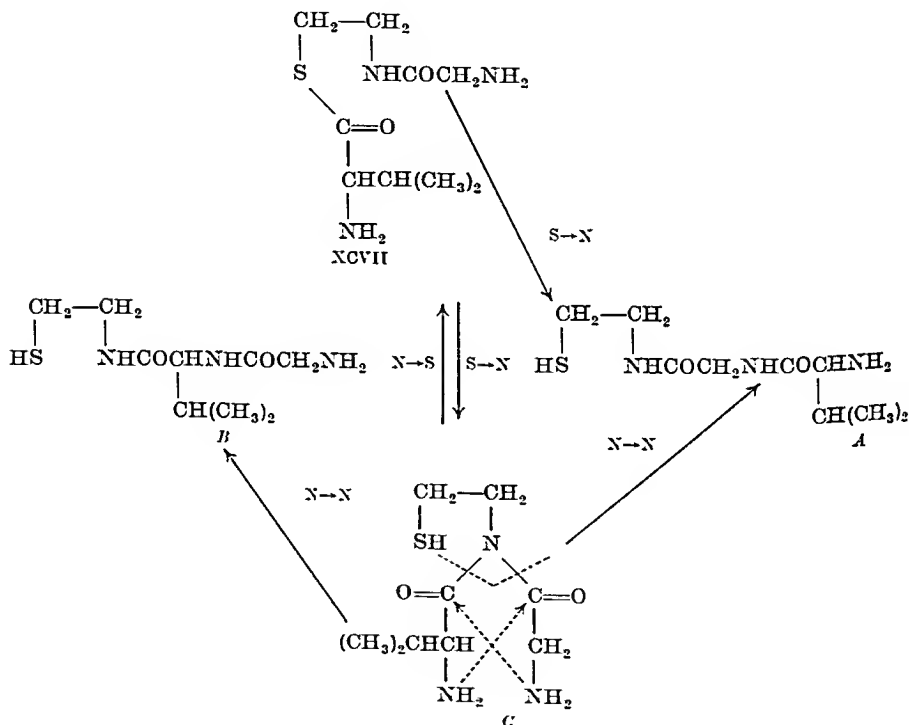
Experimental support for this reaction scheme was subsequently obtained from the observation that diglycylimide underwent an N to N migration at $pH \geqq 5$ to give diglycinamide.[364]

It is possible that the same sort of transformation might occur with glutathione in dilute solution. A reactive amino acid intermediate would be expected to react first with the thiol group to give a thiol ester. An S to N migration to the glycine nitrogen via a six-membered cyclic intermediate followed by an N to N migration of the cysteine moiety via

[364] Wieland and Mohr. *Ann.*, 599, 222 (1956).

a five-membered cyclic intermediate would lead to insertion of the amino acid into glutathione between the cysteine and glycine residues. The process can be repeated. A peptide synthesis has not been achieved with S-methionylglutathione, but the objective of previous studies was merely the use of S-amino acid glutathione derivatives for acylation of other amino acids rather than for insertion of the amino acids into the glutathione chain.

Reaction of S-valyl-N-alanylglycylcysteamine (XCVIII) with aqueous calcium carbonate gave a mixture of peptide products. The presence of N-alanylvalylglycylcysteamine among the products can be explained by assuming that the valyl group first migrates from sulfur to the neighboring amide nitrogen. An N to N migration can then place either valine or alanine in the penultimate position.[280]

$$\begin{array}{ccc} & CH_2\!-\!CH_2 & \\ & | & | \\ & S & NH \\ & | & | \\ (CH_3)_2CHCH(NH_2)CO & COCH_2NHCOCH(NH_2)CH_3 \\ & XCVIII & \end{array}$$
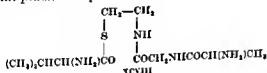
Experimental Conditions

Preparation of Thiol Esters and Thiol Acids. Although a variety of α-acylamino acid mixed anhydrides could serve as starting materials for the synthesis of thiol esters or thiol acids, the mixed alkyl carbonic anhydride has been most commonly used. The α-acylamino acid or peptide alkyl carbonate is prepared in an indifferent solvent, and the mercaptan is then added to the solution of the mixed anhydride. The subsequent procedure is similar to that used in the coupling of alkyl carbonic mixed anhydrides with amino acids or esters.

Thiosalicylic or thioglycolic acid is customarily dissolved in ethyl acetate containing an equivalent of triethylamine and added to the solution of the α-acylaminoacyl alkyl carbonate.[242, 305, 305a] After $\frac{1}{2}$ to 4 hours at room temperature, the mixture is washed with water and dilute hydrochloric acid, and concentrated to give the thiol ester. With thiophenol, a bicarbonate wash is also used. If the solvent is miscible with water, it is removed in vacuum and the residue taken up in ethyl acetate (or other water-immiscible solvent) before washing with acid and bicarbonate.

In the preparation of thiol acids, the solution of mixed carbonic anhydride is saturated with hydrogen sulfide at room temperature in the presence of one equivalent of triethylamine. After the solution has

[305] Schwyzer U S pat 2,824,863 (to Ciba) [C A , 52, 14689c (1958)]
[305a] Schwyzer, Helv Chim Acta, 37, 647 (1954)

stood overnight, the solvent is removed in vacuum, the residue taken up in water and acidified with dilute hydrochloric acid.[339, 340, 351]

When dicyclohexylcarbodiimide is used to form the acyl peptide thiophenyl ester, equivalent amounts of acyl peptide and thiophenol dissolved in a solvent such as tetrahydrofuran are treated with a 10% excess of dicyclohexylcarbodiimide. After 4 or more hours, the dicyclohexylurea is removed by filtration and the product isolated by concentrating the filtrate.[273] By this procedure, carbobenzyloxy-ε-aminocaproyl-ε-aminocaproic acid was converted to the thiophenyl ester in 89% yield.

When amino acid thiophenyl esters are employed, polymerization of the amine component is possible as it is liberated from its salt.[163, 366, 367] This is especially true of the p-nitrothiophenyl derivative.[37] To minimize this reaction, one equivalent of triethylamine is added to the mixed carbonic anhydride followed by one equivalent of the desired amino acid thiophenyl ester hydrobromide. The latter may be dissolved in chloroform or other suitable solvent. After 2 to 4 hours the product is isolated in the same manner as an α-acylamino peptide ester. Mixed anhydrides of α-carbobenzyloxyamino acids and dichlorophosphoric acid react with thiophenol and p-nitrothiophenol to give the thiophenyl esters. The best yields are obtained if the α-carbobenzyloxyamino acid, thiophenol, and phosphorus oxychloride are dissolved in tetrahydrofuran, cooled to $-15°$, and pyridine is then added. The reaction is complete after 1 hour at room temperature.[37]

Amino acid thiol esters are prepared by warming amino acid chloride hydrochlorides with excess thiophenol to 70° for 15 minutes and cooling, or by allowing the reaction to proceed several days at room temperature.[367] The addition of glycyl chloride hydrochloride to thioglycolic acid resulted in a spontaneous reaction. The mixture was then heated for 30 minutes at 70° and 20 minutes at 90°. Ethanol was added to give a clear solution. Introduction of acetone caused precipitation of S-glycylthioglycolic acid hydrochloride in 80% yield.[343]

When L-valine chloride hydrochloride was heated with one equivalent of thiophenol in benzene for 1 hour at 80° the reaction product contained diketopiperazine, dipeptide thiophenyl ester hydrochloride, and some thiophenyl esters of higher oligopeptides.[368] The use of excess thiophenol with the acid chloride hydrochloride at room temperature has been applied to the preparation of several peptides; glycyl-DL-valine, glycyl-DL-leucine, and glycyl-DL-valyl-DL-isoleucine were converted to thiophenyl ester hydrochlorides in yields of 42, 40, and 80%, respectively.[368]

Phthaloylglycyl chloride was converted to phthaloylthioglycine in good

[366] Wieland and Schäfer, *Angew. Chem.*, **63**, 146 (1951).
[367] Wieland and Schäfer, *Ann.*, **576**, 104 (1952).
[368] Wieland and Bernhard, *Ann.*, **582**, 218 (1953).

yield by reaction with sodium hydrogen sulfide in dimethylformamide.[339]

Exchange reactions between amino acid thiophenyl esters and other thiols are conducted in aqueous or ethanolic solution at weakly acid pH with excess thiol ester.[290]

p-Nitrothiophenyl carbobenzyloxyglycyl-L-phenylalanine was prepared in 99% yield by treating lithium carbobenzyloxyglycyl-L-phenylalaninate with tri-p-nitrothiophenyl phosphite in dimethylformamide at 18°.[335] p-Nitrothiophenyl esters may also be prepared by reaction of tri-p-nitrothiophenyl phosphite with an equivalent amount of carboxylic acid in dimethylformamide at 85° for 20 minutes. Pyridine may be substituted for dimethylformamide if the mixture is heated to 60° for 5 minutes and then left overnight at 18°.[34] Yields are generally high for both acylamino and acyl peptides.

The mixed sulfuric anhydrides of carbobenzyloxyglycine and of carbobenzyloxyglycyl-L-phenylalanine were used for preparation of the p-nitrothiophenyl esters in 70% and 58% yields, respectively.[28]

Amide Bond Formation. — Although acyl thiols react with amines in the absence of a solvent, the use of water, alcohols, dimethylformamide, tetrahydrofuran, or mixtures of these solvents is more usual. Concentrations are preferably one molar or more for the two reactants,[344] but reactions catalyzed by metal ions may be carried out in dilute aqueous solutions.[343] It is preferable to carry out syntheses of more complex peptides at room temperature, but the reaction of an S-acylthioglycolic or thiosalicylic acid or their esters with the sodium salt of an amino acid may be completed by warming at 80–85° or by heating under reflux in methanol for 1 hour   The solvent is removed in vacuum, the residue taken up in water, and the product precipitated by acidification.[336] This procedure, with the thiophenyl ester, gave 90% analytically pure carbobenzyloxyglycylalanine   Methanol generally gives better yields than aqueous solvents   Reaction of a thiol ester with an amino acid in neutral solution fails because the reaction produces an acid which reduces the concentration of uncharged amino groups and stops the reaction.   Pyridine may be used as a buffer with the result that good yields may be obtained in 1 hour of heating under refluxing conditions.[336]

Better results have been obtained when coupling has been conducted in the presence of sodium bicarbonate rather than sodium hydroxide. For example, carbobenzyloxy-β-alanine thiophenyl ester gave a 70% yield of pure carbobenzyloxy-β-alanyl-β-alanine when concentrated sodium bicarbonate solution was employed, but only a 50% yield of crude material with N sodium hydroxide.[326]

S-Acylthioglycolates and thiosalicylates have been used only when the acyl group was benzoylglycine or carbobenzyloxyglycine. They were

coupled with the sodium salts of amino acids and dipeptides in yields varying from 45% to 80%.

Several workers have noted that control of pH may be advisable. In the reaction of carbobenzyloxyglycylthioglycolic acid with aniline in buffered dimethylformamide solutions, yields increased from 14.5% to 66% as the pH was increased from 2 to 4 but then decreased as the pH was increased beyond pH 4. The optimum pH was found to vary with the amine. Benzylamine reacts with S-hippurylthioglycolic acid at pH 8 to give 43% and at pH 9 to give 73% of the amide.[344] The reaction of p-nitrothiophenyl esters with amino acids in dioxane solution at 18° for 18 hours gave excellent yields when buffered at an apparent pH 6.8 with excess solid magnesium carbonate.[335]

Peptide bond formation that is catalyzed by metal ions (silver, lead, copper, or mercury) requires control of the pH to obtain optimum yields. Best results are usually obtained at pH 6 to 8. S-Hippurylthioglycolic acid reacts with glycine in the presence of silver nitrate to give the maximum yield, 85%, of hippurylglycine at pH 6; the yield was only 30% at pH 8.1. However, the same components react in the presence of lead acetate to give an 80% yield at pH 8 and a 9% yield at pH 7.[363] The reaction is normally carried out by dissolving the α-acylamino acid thiol ester and the amino acid to be acylated in an aqueous medium and adding dropwise N aqueous sodium hydroxide and a solution of the metal salt (silver nitrate is best) either simultaneously or alternately to maintain the pH at the desired value. Buffered solutions have also been employed. The reaction mixture is allowed to stand at room temperature for about 15 hours to complete the reaction. If the metal has precipitated as a salt (e.g., silver thioglycolate), it is removed by filtration. Otherwise the metal catalyst is precipitated with hydrogen sulfide and removed before isolating the peptide intermediate.

Experimental Procedures

Thiophenyl Carbobenzyloxy-β-alaninate (Preparation of a Thiophenyl Ester via the Mixed Carbonic anhydride).[336] A solution of 3 g. of carbobenzyloxy-β-alanine and 1.53 g. of N-ethylpiperidine in 13.5 ml. of tetrahydrofuran was cooled to 0° and 1.5 g. of ethyl chloroformate added dropwise. N-Ethylpiperidinium chloride precipitated at once. When the odor of the acid chloride had disappeared (10–15 minutes), 1.52 g. of thiophenol was added and the mixture allowed to stand 4 hours at room temperature. The solvent was removed under reduced pressure and the residual syrup triturated with water to induce crystallization. Recrystallization from water gave 3.7 g. (90%) of product, m.p. 77°.

p-Nitrothiophenyl Carbobenzyloxyglycyl-L-phenylalaninate (Preparation of a Thiophenyl Ester via Tri-*p*-nitrothiophenyl Phosphite) [88] A solution of 1.78 g (5 mmoles) of carbobenzyloxyglycyl-L-phenylalanine in 65 ml. of dimethylformamide was neutralized with methanolic lithium methoxide and then concentrated to 50 ml. at 50° and 11 mm. under a six-inch column of steel gauze rings. The solution was cooled to 20° and treated with 1.70 g. (5 mmoles) of tri-*p*-nitrothiophenyl phosphite, which dissolved on shaking. The solution was kept overnight and then poured onto water. The product was extracted with ethyl acetate and washed successively with *N* sulfuric acid, water, sodium bicarbonate solution (twice), and water. The ethyl acetate was combined with ethyl acetate extracts of the aqueous washings and the combined extracts evaporated to dryness. The residue was recrystallized from methanol to give 79% of the thiol ester, colorless needles, m.p. 154–155°, $[\alpha]_D^{25}$ −67° ±0.2° ($c = 4.6\%$, dioxane).

Carbobenzyloxyglycyl-DL-alanine (Amide Formation in Absolute Methanol) [33a] A solution of 1.78 g. of thiophenyl carbobenzyloxyglycinate in 16 ml. of methanol containing 128 mg. of sodium and 5 g. of DL-alanine was heated under reflux for 4 hours. The solvent was removed under reduced pressure and the residue taken up in a small amount of water. Acidification of the solution to Congo red with dilute hydrochloric acid precipitated 1.4 g. (90%) of analytically pure carbobenzyloxydipeptide, m.p. 177°

In aqueous tetrahydrofuran (4 hours at 60°) the same compound was obtained, 75% yield.

Hippurylglycine (Amide Formation Catalyzed by Metal Ions) [33] To a solution of 0.243 g. of S-hippurylthioglycolic acid and 0.10 g. of glycine in 7 ml. of water was added dropwise and alternately a solution of 0.170 g. of silver nitrate in 3 ml. of water and *N* aqueous sodium hydroxide so as to maintain the pH at 6.0. The solution was diluted to 14 ml. with water and allowed to stand 15 hours at 40°. The silver thioglycolate was removed by filtration, the filtrate concentrated under reduced pressure, the residue taken up in a small amount of water and acidified to pH 2. There was obtained after recrystallization from water and washing with absolute ethanol 0.193 g. (85%) of hippurylglycine, m.p. 206–206.5°.

In the absence of silver nitrate, the yield of hippurylglycine was 46%.

α-ACYLAMINOACYL SULFATES

Sulfuric acid anhydrides were introduced in peptide synthesis early in 1951.[289] The method consists of the reaction of the salt of an α-acylamino-

[288] Kenner, *Chem. and Ind. (London),* 1951, 15

acid with sulfur trioxide to give a mixed anhydride. To this anhydride is added the sodium salt of an amino acid to give an acyl dipeptide as illustrated in the accompanying equations.

$$R_1CONHCH(R_2)CO_2Li + SO_3 \rightarrow R_1CONHCH(R_2)CO_2SO_3Li$$

$$R_1CONHCH(R_2)CO_2SO_3Li + H_2NCH(R_3)CO_2Na \rightarrow$$
$$R_1CONHCH(R_2)CONHCH(R_3)CO_2Na + LiHSO_4$$
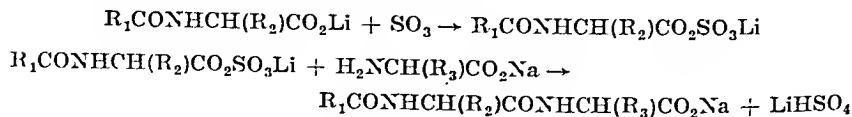
The dibasicity of sulfuric acid makes it possible to obtain the mixed anhydride in the form of a water-soluble salt. Thus acylation of the sodium salt of an amino acid can be achieved in a single-phase reaction.

The peptide-forming step involves the usual attack on the carbonyl carbon by the amine. Kenner[5] has suggested that by-products may arise because of moisture, disproportionation of the mixed anhydride, or by attack of the amine on sulfur as well as on carbon.

Disproportionation:

$$2RCO_2SO_3Li \rightarrow (RCO)_2O + Li_2S_2O_7$$

Attack on S and C:

$$RCO_2SO_3Li + H_2NR \begin{array}{c} \nearrow RCONHR + LiHSO_4 \\ \searrow RCO_2H + LiSO_3NHR \end{array}$$
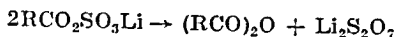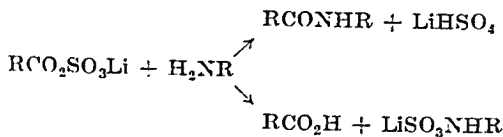
Scope and Limitations

Acyl derivatives of glycine, alanine, cystine, cysteine, tyrosine, tryptophan, and phenylalanine have been used as the α-acylamino components. The hydroxyl group of tyrosine must be protected.[370] Yields of acyl di- and tri-peptides have generally been about 60–80%. Amides of lysergic acid were also prepared.[371]

For satisfactory results alkali metal salts of the α-acylamino acid or acyl peptide must be employed. 4-Methylmorpholine salts gave very poor yields.[183] Commercially available trimethyl- and triethyl-amine sulfur trioxide complexes are unsatisfactory because they are too stable.[5]

Less than 5% of racemization was observed when the mixed anhydride of carbobenzyloxyglycyl-L-phenylalanine and sulfuric acid was coupled with glycine at pH 7.4, but considerable racemization was observed at pH 9. Earlier experiments had indicated that racemization was caused by aqueous alkali and not during the anhydride-forming step.[183] Coupling the anhydride of sulfuric acid and carbobenzyloxyglycyl-L-alanine with

[370] Clayton, Farrington, Kenner, and Turner, J. Chem. Soc., 1957, 1398.
[371] Garbrecht, U.S. pat. 2,774,763 (to Eli Lilly) [C.A., 51, 6710f (1957)].

L-phenylalanylglycine at pH 7.4 gave a ratio of LL to DL tetrapeptide of 62 1. The products were separated by countercurrent distribution.[8] It was suggested that formation of the tetrapeptide was a slower reaction than that of the tripeptide, so that more racemization and hydrolysis occurred with the former. The tetrapeptide was formed in 60% yield, the carbobenzyloxyglycyl L-phenylalanylglycine in 83% yield. Subsequent work showed that, if the pH was kept below 6.8 by powdered magnesium carbonate, less than 1° of the tetrapeptide was racemized.[270]

When esters were substituted for the sodium salts of amino acids and the reactions carried out in dry dimethylformamide, no racemization was observed.[8,270] The use of esters in inert solvents obviates the necessity for control of pH, a mole of triethylamine is merely added to the reaction mixture.

The sulfuric acid mixed anhydride will not acylate an amide even intramolecularly.[8] This observation may prove of some value in the synthesis of peptides of asparagine or glutamine.

The sulfuric anhydride procedure has been extended to cyclic anhydrides of sulfonic and carboxylic acids (pp. 198-199). However, relatively poor results were obtained with α-sulfobenzoic anhydride, 3,5-dibromo-2-sulfobenzoic anhydride, and β-sulfopropionic anhydride in model experiments with p-toluenesulfonyl-DL-alanine and morpholine.[185] Furthermore, the intermediates are probably carboxylic acid mixed anhydrides and not sulfonic acid mixed anhydrides. Propane 1,3-disulfonic anhydride gave only a 27% yield of p-toluenesulfonyl-DL-alanine morpholinide.[187] The mixed anhydrides of α-acylamino acids prepared from these cyclic sulfonic anhydrides probably disproportionate readily or, more likely, are attacked at both points by the amine.

The mixed anhydride prepared from carbobenzyloxyglycine and sulfuryl chloride, when treated with sodium glycinate in tetrahydrofuran at 0° in the presence of N-ethylpiperidine, gave carbobenzyloxyglycylglycine in only 30% yield.[8] Probably disproportionation caused the low yield. Substitution of thionyl chloride for sulfuryl chloride served to increase the yield of product to 35%.

The sulfuric anhydride method is patented.[272-276]

Experimental Conditions

The mixed anhydride is prepared by adding sulfur trioxide in the form of its crystalline dimethylformamide complex to the alkali metal salt of

[270] Kenner, Brit. pat. 714,836 (to Natl Res Dev Corp) (1954)
[272] Fr. pat. 1,048,050 (to Natl Res Dev Corp) [Chem. Zentr., 127, 8986 (1956)]
[273] Kenner, Swiss pat. 314,637 (to Natl Res Dev Corp) [Chem. Zentr., 128, 7251 (1957)].
[274] Kenner, Swiss pat. 314,637 (to Natl Res Dev Corp) [C.A., 51, 2633f (1957)]
[275] Kenner, U.S. pat. 2,786,723 (to Natl Res Dev Corp)
[276] Kenner, Ger. pat. appl. 1,003,742 (to Natl Res Dev Corp)

the α-acylamino acid or peptide in dimethylformamide, a particularly useful solvent for this reaction.

Alternatively, a solution of known normality of the sulfur trioxide-dimethylformamide complex in dimethylformamide may be introduced into the cold solution of the salt of the α-acylamino acid or peptide.

Sulfur trioxide was formerly prepared from sulfur dioxide and oxygen in the presence of a platinum catalyst at 650° and distilled twice before conversion to the dimethylformamide complex. Sulfur trioxide prepared from oleum usually contained traces of moisture and gave lower yields than that prepared from sulfur dioxide unless the dimethylformamide complex was purified by recrystallization.[5] The complex may be stored for several months in a refrigerator.[183, 370] Sulfur trioxide-dioxane or sulfur trioxide-pyridine complexes do not give satisfactory results.

The salt of the α-acylamino acid or peptide is prepared by exact neutralization of the acid in dimethylformamide with potassium methoxide or with phenyltrimethylammonium methoxide in methanol followed by removal of the methanol in vacuum at 50°.[369, 372, 373] On drying the phenyltrimethylammonium salts, some decomposition to dimethylaniline and the methyl ester of the carboxylic acid was observed.[370] Lithium methoxide is now favored for neutralization[5, 36, 370] because of the relatively high solubility of lithium salts of α-acylamino acids or peptides in organic solvents.[375]

The reaction of the sulfur trioxide-dimethylformamide complex with the potassium or lithium salt of the α-acylamino acid in dimethylformamide is complete within 1 minute at 0°. The stability of the mixed anhydride with respect to disproportionation was investigated by the preparation of tosyl-DL-alanylcyclohexylamide. Quantitative yields of amide were obtained when the mixed anhydride was allowed to stand for 3 to 130 minutes before the addition of the amine.[183]

The mixed α-acylamino sulfuric anhydrides are fairly stable at pH 7, but not at higher pH. For example, the half-life of carbobenzyloxyglycyl lithium sulfate in 40% dimethylformamide containing potassium phosphate varied from 10.5 hours at pH 6 to about 1 hour at pH 9 and about 0.1 hour at pH 10.[5] During the reaction of the mixed anhydride with the aqueous amino acid solution the pH is controlled either by the use of a buffer such as powdered magnesium carbonate, or by the addition of alkali to maintain the pH between 7.4 and 8.5, using phenol red as an indicator.[370] When magnesium carbonate is used, stirring is continued for 15 hours. Excess magnesium carbonate is then dissolved with hydrochloric acid. When sodium hydroxide is employed, the reaction mixture may be worked up 15 minutes after the addition of the anhydride. In reactions in anhydrous dimethylformamide, the reaction is allowed to proceed for 1 hour at 20°.

In most cases in which sulfuric acid mixed anhydrides have been employed for peptide synthesis, coupling has been between an α-acylamino acid or acyl peptide and an amino acid sodium salt so that purification has necessitated the use of countercurrent distribution An eleven or twenty-two transfer distribution between ethyl acetate and molar phosphate buffer has proved satisfactory.[183, 369, 372, 373]

Experimental Procedures

Sulfur Trioxide-Dimethylformamide Complex.[183] Sulfur trioxide is distilled directly onto the surface of dimethylformamide which is stirred and cooled in an ice bath When crystals start to separate, distillation is stopped and dimethylformamide added to give a clear solution which is standardized by titration with aqueous alkali.

Preparation of Anhydrous Salts of α-Acylamino Acids.[183] Two to ten millimoles of the α-acylamino acid is dissolved in 30 to 50 ml. of dimethylformamide and the solution neutralized with methanolic potassium methoxide or lithium methoxide. About half of the solvent is removed by distillation at 50°/15 mm through a 15-cm. packed column. Phenyltrimethylammonium salts may also be used They are prepared by neutralizing the α-acylamino acid with the filtrate from the reaction of phenyltrimethylammonium p-toluenesulfonate with methanolic sodium methoxide

Carbobenzyloxyglycyl-DL-phenylalanine.[183, 372, 373] A solution of 10 mmoles (6.6 ml) of the sulfur trioxide-dimethylformamide complex in excess dimethylformamide was added to 10 mmoles of potassium carbobenzyloxyglycinate in dimethylformamide and the reaction mixture shaken at 20° for 5 minutes before it was cooled in an ice-salt bath. A solution of 1.98 g (12 mmoles) of DL-phenylalanine in 10 ml of water and 12 ml. of aqueous sodium hydroxide containing phenolphthalein was added with stirring in one portion to the solution of the mixed anhydride. Sufficient 0 5N aqueous sodium hydroxide was then rapidly added to restore and maintain the pink color. After 10 minutes the solution was neutralized with 3N sulfuric acid and evaporated under reduced pressure to a syrup which was taken up in 12 ml of 3N sulfuric acid and 50 ml. of ethyl acetate The layers were separated and the aqueous layer extracted four times with ethyl acetate. The ethyl acetate extracts were combined, dried, and concentrated to give 5.15 g. of pale yellow oil An eleven-transfer distribution between ethyl acetate and 3M phosphate buffer (7 moles of potassium dihydrogen phosphate to 3 moles of dipotassium hydrogen phosphate) gave 2 5 g (70%) of product and 0.7 g. (3 mmoles) of carbobenzyloxyglycine. Recrystallization of the product from ethyl acetate gave colorless needles, m p 162°

The use of phenol red rather than phenolphthalein to control the pH gives better results with optically active amino acids.[370]

α-ACYLAMINOACYL ALKYL AND ARYL SULFONATES

Although it has been reported that benzene- or p-toluene-sulfonyl chloride cannot be used for the synthesis of peptides,[48] these chlorides have been successfully used in such syntheses.[377] Methanesulfonyl chloride is equally satisfactory, but sulfenyl and sulfinyl chlorides gave poor results. The synthesis of methyl carbobenzyloxy-DL-tryptophyl-β-alaninate is illustrated in the accompanying equations. The two-step
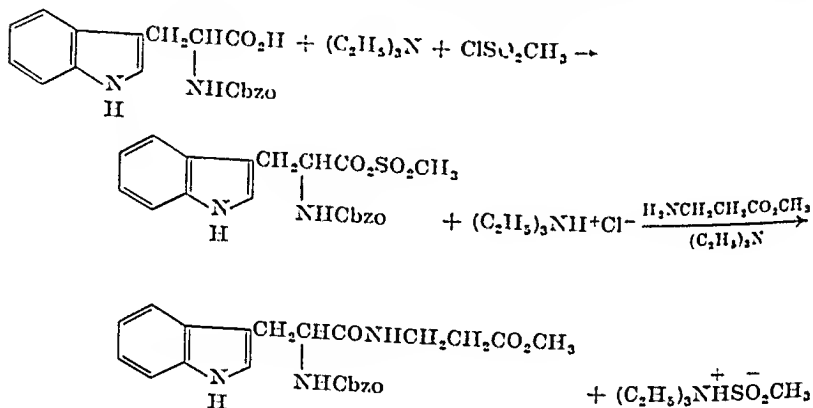
reaction, which is carried out without isolation of the mixed anhydride, requires a mole of base for each step.

The isolation of a crude mixed anhydride[15] affords partial support of the postulated course of reaction. The reaction has also been conducted by adding benzenesulfonyl chloride to a mixture of the α-acylamino acid and amino acid ester in pyridine;[378] the reaction is assumed to proceed by way of the symmetrical anhydride.

Scope and Limitations

Both the scope of and the yields obtained with the sulfonyl chloride procedure appear to be comparable to those with the chloroformate procedure. Reaction of L-proline in aqueous acetone with p-toluene-sulfonyl chloride in the presence of sodium bicarbonate gave, in addition

[377] F. C. McKay. Unpublished results.
[378] Sokolowska, Kupryszewski, and Taschner, *Bull. acad. polon. sci., Classe III*, **6**, 89 (1958) [*C.A.*, **52**, 16236g (1958)].

to a 77% yield of p-toluenesulfonyl L-proline, a 6% yield of p-toluene-sulfonyl L-prolyl-L-proline.[373] A mixed anhydride between p-toluene-sulfonyl L-proline and p-toluenesulfonic acid was presumably formed in the aqueous solution

The modification employing pyridine as a solvent[373] failed with hippuric acid and gave side reactions with carbobenzyloxyamino acids, but phthaloyl and tosyl dipeptide esters were obtained in 50% to 90% yield.

Experimental Conditions

A solution of the α-acylamino acid and one equivalent of triethylamine in an inert solvent such as acetone or toluene is cooled normally at −10° with methanesulfonyl chloride and to 0° with p-toluenesulfonyl chloride or benzensulfonyl chloride. The reaction mixture is then stirred for 3 to 30 minutes, and the amine to be acylated is added, usually in solution in a suitable solvent such as acetone, water, or chloroform. An additional mole of triethylamine is also added. If an amino acid ester hydrochloride is used, two additional moles of triethylamine are used.

The amide-forming step is allowed to proceed for 2 hours at room temperature, or the reaction mixture is warmed to 65-70° for 5 minutes, cooled, and worked up. The isolation procedure is the same as for the products formed by the mixed alkyl carbonate method

The reaction also proceeds satisfactorily when the α-acylamino acid and amino acid ester are dissolved in dry pyridine and one equivalent of benzenesulfonyl chloride is added. The product is isolated by diluting the reaction mixture with water after 1 to 20 hours at room temperature.[373]

Experimental Procedures

Methyl Carbobenzyloxy-L-leucyl-L-leucinate.[377] A solution of 25 g. of carbobenzyloxy-L-leucine and 13.2 ml. of triethylamine in 200 ml. of acetone was cooled to −10° and treated with 7.2 ml. of methanesulfonyl chloride. The mixture was stirred for 4 minutes at −10° to form the mixed anhydride. To this solution were added 17.2 g. of methyl L-leucinate hydrochloride and 26.4 ml. of triethylamine in 75 ml. of chloroform, and the mixture was allowed to warm to room temperature. Stirring was continued for 2 hours, the mixture was filtered, the solvent removed by distillation, and the residue taken up in ethyl acetate. The ethyl acetate solution was washed successively with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and again with water The ethyl acetate layer was dried and concentrated and the residue recrystallized from ethyl acetate-n-hexane to give 26.8 g. (73%) of methyl

carbobenzyloxy-L-leucyl-L-leucinate, m.p. 73–81°; $[\alpha]_D^{25}$ −35.8 ± 0.2°
(c = 1%, ethanol).

Ethyl Carbobenzyloxyglycyl-L-leucyl-D-tryptophanate.[15] To a
solution of 8.1 g. of carbobenzyloxyglycyl-L-leucine and 7 ml. of triethyl-
amine in 70 ml. of toluene, cooled to 0°, was added 4.8 g. of p-toluene-
sulfonyl chloride and the mixture was stirred for 30 minutes. To the
solution of the mixed anhydride was added a solution of 6.6 g. of ethyl
D-tryptophanate in 40 ml. of warm toluene. The mixture was heated
rapidly to 65°, kept at this temperature for 5 minutes, and then cooled.
The solution was successively washed with water, dilute hydrochloric
acid, and aqueous sodium bicarbonate and the solvent removed to give
7.1 g. of product, m.p. 127–130°.

α-ACYLAMINOACYL PHOSPHATES

The α-acylaminoacyl phosphates that have been used for peptide
synthesis have the general formula XCIX, where $R_1CONHCHR_2CO$ is an

$$R_1CONHCHR_2\overset{\overset{\displaystyle O}{\|}}{C}OP \underset{OR_4}{\overset{OR_3}{\diagup\!\!\!\searrow}} O$$

XCIX
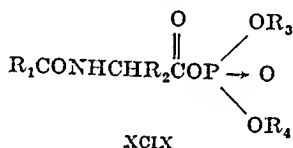
acylated amino acid and R_3 and R_4 are both ethyl, phenyl, or benzyl, or
one is silver and one is phenyl. Mixed anhydrides of 2′,3′-isopropyli-
deneadenosine-5′-benzylphosphoric acid with carbobenzyloxyamino acids
such as C have also been used.[380]

Although the α-acylaminoacyl phosphates are of interest biochemically,
they have not proved to be of practical utility in the synthesis of peptides.

C
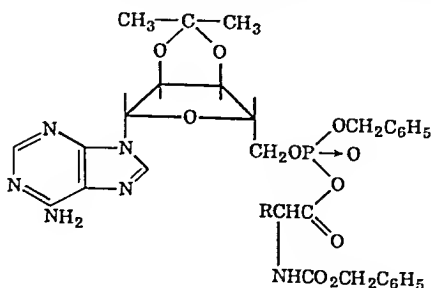
[380] Shabarova, Satarova, and Prokof'ev, *Doklady Akad. Nauk S.S.S.R.*, **123**, 864 (1958)
[C.A., **53**, 10231c (1959)].

In general, anhydrides of phosphoric acid or its mono- or di-alkyl derivatives with α-acylamino acids are not so readily prepared as a number of other mixed anhydrides. Furthermore, the necessary phosphate must itself be synthesized before it can be converted to the α-acylaminoacyl phosphate, and the use of the α-acylaminoacyl chloride for the preparation of the aminoacyl phosphate adds an additional step. The use of esters of the enol phosphate of malonic acid to synthesize α-acylaminoacyl phosphates[341-343] might increase the utility of phosphate anhydrides.

Scope and Limitations

Use of an α-Acylamino Acid Mixed Anhydride and a Phosphate Salt. The use of α-acylamino acid mixed phosphates was designed to test the suggestions of Lipmann[344] that acyl phosphates supplied the energy necessary for peptide bond formation *in vivo*. Except for the use of enol phosphates, the work has been largely limited to model experiments with carbobenzoxy- and phthaloyl-glycine.

Carbobenzyloxyglycyl chloride reacts with disilver phenyl phosphate to give silver phenyl carbobenzyloxyglycyl phosphate[22,345]. This anhydride is fairly stable for several hours in aqueous solution at pH 7.4 at 37° but reacts rapidly with glycine to give carbobenzyloxyglycylglycine in high yield. The reaction was carried out on a very small scale, and the products were identified by paper chromatography.

Hydrogenolysis of silver phenyl carbobenzyloxyglycyl phosphate at pH 7.4 resulted in a mixture of dipeptide and diketopiperazine, while at pH 3.0 it gave phenyl glycyl phosphate as shown by reaction of the product with hydroxylamine.

Phthaloylglycyl chloride reacts with silver dibenzyl phosphate to give dibenzyl phthaloylglycyl phosphate. This mixed anhydride in benzene readily disproportionates when heated or upon long standing. The addition of triethylamine caused rapid disproportionation[345]

Dibenzyl phthaloylglycyl phosphate reacts rapidly and exothermically with aniline to give phthaloylglycylanilide in 91% yield[345]. There was no evidence that the mixed anhydride had reacted to give N-(dibenzylphosphoryl)aniline. Dibenzyl phthaloylglycyl phosphate also acylates DL-phenylalanine and glycine to give the phthaloyldipeptides in 83% and 91% yields, respectively.

341 Cramer and Gartner, *Chem. Ber.* **91**, 1562 (1958).
342 Cramer and Gartner, 4th Intern. Congr. Biochem., Vienna Sept. 1–6, 1958, Abstracts, Sect. 1, No. 10.
343 Cramer and Gartner, *Chem. Ber.* **91**, 704 (1958).
344 Lipmann, *Advances in Enzymol.* **1**, 163 (1941).
345 Chantrenne, *Nature*, **164**, 576 (1949).
346 Sheehan and Frank, *J. Am. Chem. Soc.* **72**, 1312 (1950).

The reaction of phthaloylglycyl chloride with triethylammonium dibenzyl phosphate gave only the symmetrical anhydrides.[386]

Carbethoxyglycyl phosphate was prepared from carbethoxyglycyl ethyl carbonate and phosphoric acid, but no amides were prepared from this mixed anhydride.[387] α-Azidoamino acid chlorides react with silver dibenzyl phosphate to give nearly quantitative yields of the mixed anhydrides of the glycine, DL-alanine, and DL-phenylalanine analogs.[388] Hydrogenation in the presence of Raney nickel reduced the α-azido group and further reduction with a palladium catalyst removed the benzyl groups. The mixed anhydrides were isolated as the disilver and also as the neutral barium salts in about 50% yield.

The mixed adenylic acid DL-valine anhydride (valyl AMP) has been prepared in 10–20% yield by warming the sodium salt of adenosine-5'-phosphoric acid with thiophenyl-DL-valinate hydrochloride in dimethylformamide for half an hour at 120°.[389] The synthesis of L-leucyl adenosine-5-phosphate was achieved in 9% yield from L-leucyl chloride hydrochloride and disilver adenosine monophosphate in acetic acid.[390]

Use of an α-Acylamino Acid Salt and a Phosphate Mixed Anhydride. The conversion of an α-acylamino acid directly to a phosphate anhydride without the prior formation of an intermediate acylamino acid anhydride is a prerequisite for any practical phosphate mixed anhydride synthesis. The use of an enol phosphate of malonic ester achieves this.

An α-acylamino acid will react with α-ethoxy-β-carbethoxyvinyl diethyl phosphate (CI) to give an α-acylaminoacyl diethyl phosphate CII and diethyl malonate.[381,382,391]

$$R_1CONHCHR_2CO_2H + (C_2H_5O)_2\overset{O}{\underset{CI}{P}}{-}O{-}\overset{OC_2H_5}{\underset{}{C}}{=}CHCO_2C_2H_5 \rightarrow$$

$$R_1CONHCHR_2CO_2\overset{O}{\underset{CII}{P}}(OC_2H_5)_2 + CH_2(CO_2C_2H_5)_2$$
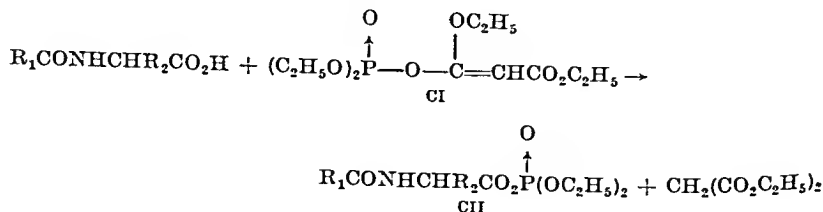
Carbobenzyloxy derivatives of glycine, DL-alanine, and L-leucine have been converted to diethyl phosphate mixed anhydrides and used to acylate the esters or sodium salts of amino acids and peptides. Over-all

[387] Avison, *J. Chem. Soc.*, 1955, 732.
[388] Bentler and Netter, *Z. physiol. Chem., Hoppe-Seyler's*, 295, 362 (1953).
[389] Wieland, Niemann, and Pfleiderer, *Angew. Chem.*, 68, 305 (1956).
[390] De Moss, Genuth, and Novelli, *Proc. Natl. Acad. Sci. (U.S.)*, 42, 325 (1956).
[391] Cramer and Gärtner, *Chem. & Ind. (London)*, 1958, 560.

yields of product varied from 61% to 87% This method would be expected to be accompanied by racemization when it is possible

The enol phosphate CI can be prepared from triethyl phosphite and bromomalonic ester and stored [263] This is the only feasible method so far developed for the synthesis of α-acylaminoacyl phosphates.

Silver carbobenzyloxy-L-leucinate reacts with 2',3'-isopropylidene-adenosine-5'-benzyl chlorophosphonate in a mixture of benzene, acetonitrile, and dioxane to give the mixed anhydride C [R = $(CH_3)_2CHCH_2$] as an oil. This oil acylated methyl glycinate to give methyl carbobenzyloxy-L-leucylglycinate. Methyl carbobenzyloxyglycyl-L-phenylalaninate was similarly prepared from silver carbobenzyloxyglycinate and methyl L-phenylalaninate [260]

An attempt to prepare dibenzyl phthaloylglycyl phosphate from silver phthaloylglycinate and dibenzyl chlorophosphate was unsuccessful, [265] the more reactive diphenyl carbobenzyloxyglycyl phosphate was successfully prepared from the N-ethylpiperidinium salt of carbobenzyloxyglycine and diphenyl chlorophosphate in tetrahydrofuran [44] The anhydride was not isolated but was treated with sodium glycinate to give carbobenzyloxy-glycylglycine in 10% yield. The low yield was attributed to the difficulty of separating the product from diphenylphosphoric acid If an ester instead of the sodium salt of the amino acid were used this difficulty might be avoided, but disproportionation might then lead to a low yield of product.

The intermediate formation of acylpeptide diphenyl phosphates such as CIII has been postulated in the reaction of acylpeptide anions with diphenyl isothiocyanophosphate (CIV). [16] The acyl diphenyl phosphate reacts with isothiocyanate ion to give a new anhydride CV which cyclizes.

$$R_1CONHCHR_2CO_2^- + (C_6H_5O)_2PO(NCS)_2$$
$$CIV$$

$$R_2CONHCHR_2CO_2PO(OC_6H_5)_2 + NCS^-$$
$$CIII$$

$$\downarrow$$

$$-OPO(OC_6H_5)_2 + R_1CONHCHR_2CONCS$$
$$CV$$

$$\downarrow$$

$$\begin{array}{c} R_1CON \quad CHR_2 \\ | \qquad \quad | \\ S=C \qquad C=O \\ \backslash \quad N \quad / \\ | \\ H \end{array}$$
$$II$$

Actually, the direct preparation of the acyl isothiocyanate CV from the acylpeptide and diphenyl isothiocyanophosphate (CIV) might well be the principal reaction. This synthesis of a diphenyl acylpeptide phosphate was designed to be used in peptide degradation rather than synthesis. While the slowness of the cyclization step would permit an amino acid ester to react with the various anhydrides in solution, the acyl isothiocyanate CV would be expected to add rather than acylate the first mole of amine.

$$R_1CONHCHR_2CONCS + H_2NCH_2CO_2CH_3 \rightarrow$$
$$R_1CONHCHR_2CONHCSNHCH_2CO_2CH_3$$
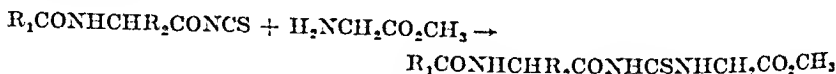
The possibility of an α-acylamino acid reacting with a tetraalkyl pyrophosphate to give an α-acylaminoacyl phosphate ester that could be employed in peptide synthesis was investigated (unpublished work, but see ref. 19). However, tetrabenzyl-, tetraphenyl-, and tetra-p-nitrophenyl-pyrophosphates gave disappointing results with tosylalanine and cyclohexylamine in model experiments. The authors state that "presumably in the basic medium the acyl phosphates are rapidly brought into equilibrium with the two symmetrical anhydrides." If this is the reason for the poor results, the symmetrical α-acylamino acid anhydride should give a 50% yield of amide plus a 50% recovery of the α-acylamino acid. The acid could then react with more tetraphenyl pyrophosphate to give ultimately another 50% yield of amide. If, however, the amine reacts with either the mixed anhydride or the pyrophosphate to give a diester phosphate amide, no further peptide bond formation would occur.[392]

The reaction of benzoyl-DL-α-glutamylglycine cyclohexylamide (CVI) with one equivalent of tetraethyl pyrophosphate gave a 67% yield of the imide CVII. The use of two equivalents of tetraethyl pyrophosphate

$$C_6H_5CONHCHCONHCH_2CONHC_6H_{11}$$

CH₂CH₂CO₂H
CVI

$$C_6H_5CONHCHCONCH_2CONHC_6H_{11}$$

CH₂   CO

CH₂
CVII
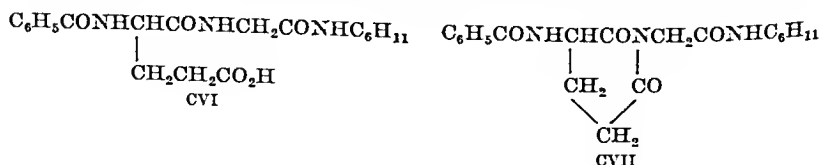
increased the yield of imide to 89%, but the recovery of the product was complicated by the presence of excess pyrophosphate.[393] The same product, CVII, was obtained in 99% yield with thionyl chloride in pyridine, in 95% yield with ethyl chloroformate, in 76% yield with excess

[392] Anderson, Blodinger, Young, and Welcher, *J. Am. Chem. Soc.*, **74**, 5304 (1952).

[393] Clayton, Kenner, and Sheppard, *J. Chem. Soc.*, **1956**, 371.

cold acetic anhydride, and in only 6% yield with the sulfur trioxide-dimethyl-formamide complex. The yield of product CVII exceeds 50% when tetramethyl pyrophosphate is used, although no amine is present to remove the phosphate as a diester phosphate amide. It is not yet understood why the use of tetraalkyl pyrophosphates gives poor yields in peptide synthesis.

α-Acylamino acid anhydrides of phosphone acid rather than its esters have been prepared, but these anhydrides have not been used for the controlled synthesis of peptides. Phthaloylglycyl chloride and alanyl chloride* react with monosilver phosphate to give phthaloylglycyl and alanyl phosphates.[351] Phosphate anhydrides of glycine,[354] alanine,[355] and leucine,[355, 356] and the β- and γ-glutamic anhydrides of L-aspartic and L-glutamic acids[356] have been prepared from the silver salt of the carbobenzyloxyamino acid and dibenzyl chlorophosphate, the three benzyl groups are removed from the intermediate dibenzyl carbobenzyloxyaminoacyl phosphates with anhydrous hydrogen bromide in carbon tetrachloride. In neutral aqueous solution the monoamino monocarboxylic acid phosphates are rapidly hydrolyzed and polymerized, whereas L-β-aspartyl phosphate and L-γ-glutamyl phosphate do not polymerize readily. The results are in marked contrast to those obtained with amino thiol acids. α-Amino thiol acids ($^{\ominus}H_3NCHRCOS^{\ominus}$), existing in the zwitter ion form, are unreactive toward ammonia or other amino acids.[351] The work of Chantrenne[22] suggests that amino acid phosphates[355, 356] might react faster with peptides than with themselves, but a controlled peptide synthesis still would not be feasible.

Alanine phosphate* was partly converted to the cyclic anhydride CVIII on drying in vacuum.

$$H_2CCH——CO$$
$$HN \qquad NH$$
$$P$$
$$O \quad O \quad OH$$
CVIII

L-β-Aspartyl phosphate and L-γ-glutamyl phosphate react with aqueous ammonia to give L-asparagine and L-glutamine, respectively, in 90% yield, so that it is reasonable to assume that these anhydrides could be used for the preparation of L-β-aspartyl or γ-glutamyl peptides. Contamination

354 Cersayon-Gentil and Nguyen Van Thoai, Compt. rend., 238, 1051 (1954)
355 Katchalsky and Paecht, Bull Research Council Israel, 2, 312 (1952)
356 Katchalsky and Paecht, J. Am Chem Soc., 76, 6042 (1954)

of the product with some of the α-isomer might occur under some conditions since the reaction could proceed at least in part through the amino acid anhydride.

Experimental Conditions

Preparation of the Mixed Anhydride. Carbobenzyloxyamino acids react with α-ethoxy-β-carbethoxyvinyl diethyl phosphate in warm dry acetone to give nearly quantitative yields of diethyl carbobenzyloxyamino acid phosphate. The reaction may also be conducted in dimethylformamide at 40° for 24 hours or at 70° for 1 hour.[381]

Phthaloyl- or carbobenzyloxy-glycyl chloride reacts with silver phosphates in ether or benzene when shaken for a few hours at room temperature. Shaking carbobenzyloxyglycyl chloride with disilver phenyl phosphate[397] for 2 hours in ether gives silver phenyl carbobenzyloxyglycyl phosphate.[22] When equimolar amounts of phthaloylglycyl chloride and silver dibenzyl phosphate were shaken in benzene for 4 hours, a 25% molar excess of the silver salt added, and the mixture shaken for an additional 2 hours, crystalline dibenzyl phthaloylglycyl phosphate was obtained in 91% yield.[386] The azido acid chlorides corresponding to glycine, DL-alanine, and DL-phenylalanine gave nearly quantitative yields of the mixed anhydrides when the chlorides were shaken with silver dibenzyl phosphate in benzene for three days at room temperature.[388] The reaction of phthaloylglycyl chloride with triethylammonium dibenzyl phosphate in benzene gave a 58% yield of phthaloylglycine anhydride based upon the chloride. A 71% yield of tetrabenzyl pyrophosphate was also isolated.[386] Carbobenzyloxyglycyl chloride reacted with pulverized silver dibenzyl phosphate at 4° overnight (shaking for the first half hour) to give a 50% yield of crystalline carbobenzyloxyglycyl dibenzyl phosphate.[386] Carbethoxyglycyl phosphate was prepared via the mixed carbonic anhydride.[387] The addition of diphenyl chlorophosphonate to a cold (0°) solution of carbobenzyloxyglycine in tetrahydrofuran containing one equivalent of N-ethylpiperidine gave a solution of diphenyl carbobenzyloxyglycyl phosphate which can be used as such.[48]

Preparation of Amide The amide-forming step is conducted by mixing solutions of the α-acylaminoacyl phosphate and the salt of an amino acid at room temperature. The latter solution is preferably buffered at pH 7.4. Dibenzyl phthaloylglycyl phosphate in dioxane was allowed to stand for 16 hours with two equivalents of glycine in a boric acid-borax buffer of pH 7.4. Removal of the solvent and recrystallization from ethanol afforded a 78% yield of pure phthaloylglycylglycine. In similar manner, crude phthaloylglycyl-DL-phenylalanine was obtained

[397] Chantrenne, *Biochim. et Biophys. Acta*, **2**, 286 (1948).

from dibenzyl phthaloylglycyl phosphate and DL-phenylalanine in 83% yield. Here again a 100% excess of amino acid was employed.

Silver phenyl carbobenzyloxyglycyl phosphate reacts rapidly with glycine, tryptophan,* and glycyltryptophan at 37° in dilute aqueous solution of pH 7.4.[1] These reactions were performed with milligram quantities and the products were not isolated. With larger quantities, countercurrent distribution would probably be needed to obtain pure products. At a pH of 6-8, the yields were 90% in a solution 0.01M with respect to the amino acid or peptide, and nearly 100% at 0.1M. These do not represent yields of isolated products, however.

Carbobenzyloxyamino acids react with α-ethoxy-β-carbethoxyvinyl diethyl phosphate to give a nearly quantitative yield of diethyl carbobenzyloxyamino acid phosphate when warmed in dry acetone or dimethylformamide at 40° for 24 hours or at 70° for 1 hour[10]

Experimental Procedures

Dibenzyl Phthaloylglycyl Phosphate.[10] A solution of 2.73 g (12 mmoles) of phthaloylglycyl chloride in 100 ml. of dry benzene was shaken with 4.65 g. (12 mmoles) of silver dibenzyl phosphate for 4 hours at room temperature. A second portion of the silver salt (1.16 g, 25% molar excess) was added and the suspension was shaken for two additional hours. The benzene solution was filtered through Celite to remove silver salts and the filtrate concentrated by freeze-drying. The residue crystallized on seeding. (A previous experiment gave a crystalline product after 4 days at room temperature.) The product was triturated with 20 ml. of dry ether, then with 20 ml. of dry ether containing 5 ml. of dry benzene, and finally with 20 ml. of dry ether. Dibenzyl phthaloylglycyl phosphate (5.11 g., 91%) was obtained as small needles, m.p. 63-65°.

Phthaloylglycylglycine.[10] A solution of 1.09 g. (2.34 mmoles) of a dibenzyl phthaloylglycyl phosphate in 10 ml. of dioxane was added to a solution of 0.353 g. (4.7 mmoles) of glycine in 10 ml. of a boric acid-borax buffer (prepared by adding 0.05M borax to 0.2N boric acid to pH 7.4). About 5 ml. of dioxan was added to effect solution. The mixture was allowed to stand for 16 hours, concentrated under reduced pressure, and the residue recrystallized from ethanol to give 0.51 g. (53%) of crude product, m.p. 180-190°. Recrystallization from ethanol yielded 0.478 g. (78%) of phthaloylglycylglycine, m.p. 229-231°. The mother liquor yielded additional product which, after recrystallization, weighed 0.08 g. (13%), m.p. 227-230°.

---

* The tryptophan was of unspecified optical configuration.

dichlorophosphate and not via a derivative of the α-amino group [130] The latter type of compound has been shown to give tris-amido compounds which react very slowly with α-acylamino acids [217]

One mole of phosphorus oxychloride per mole of α-acylamino acid gives the maximum yield of product, showing that only one chlorine atom participates in the synthesis of the anhydride. The equations for the preparation of methyl carbobenzyloxyglycylglycinate are therefore the following.

$$CzoNHCH_2CO_2H + POCl_3 + (C_2H_5)_3N \rightarrow$$

$$\underset{CIX}{CzoNHCH_2CO\overset{\overset{O}{\|}}{P}\overset{\overset{O}{\|}}{Cl}F} + (C_2H_5)_3NHCl$$

$$CIX + H_2NCH_2CO_2CH_3 \rightarrow CzoNHCH_2CONHCH_2CO_2CH_3 + Cl_2PO(OH)$$
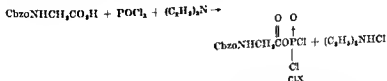
The mixed anhydride CIX will acylate the nitrogen atom of carbobenzyloxyglycine to give N,N'-dicarbobenzyloxyglycine (CX). This reaction has been observed only with glycine, [130] presumably because of the lack of steric hindrance with this amino acid

$$\underset{CX}{C_6H_5CH_2OCONHCH(CON(CH_2CO_2H)OCOCH_2C_6H_5)}$$
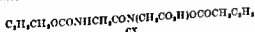
Pyruvic acid forms a mixed anhydride with phosphorus oxychloride which permits the preparation of pyruvoylamino acid esters. [119, 223]

Experimental Conditions

Three procedures have been employed for the synthesis of peptides with phosphorus oxychloride. [130] The preferred procedure follows. To a cooled solution, −15°, of 0.01 mole of α-acylamino acid and 0.01 mole of amino acid ester in 50 ml. of tetrahydrofuran is added with shaking 0.01 mole of phosphorus oxychloride followed immediately by 0.02 mole of triethylamine. One hour is allowed for completion of the reaction. Pyridine may be used in place of triethylamine, sometimes with improved yields. [27]

α-ACYLAMINOACYL PHOSPHITES

The reaction of a mono- or di-halophosphite or a tetraalkyl pyrophosphite with an α-acylamino acid leads to an α-acylaminoacyl phosphite.

[217] Wieland, Shin, and Heinke, Chem. Ber., 91, 483 (1958)

Diethyl α-Ethoxy-β-carbethoxyvinyl Phosphate.[383] An ice-cold solution of 6.2 g. of triethyl phosphite in two volumes of ethyl ether was added dropwise with stirring to an ice-cold solution of 9 g. of diethyl bromomalonate in two volumes of ether. The reaction mixture should be colorless at the end of the addition; the use of impure starting materials or too rapid addition of the triethyl phosphite produces a yellow color. The ether was removed under reduced pressure and the residue distilled with caution because of initial foaming. The main fraction distilled at 124–126°/0.05 mm.; $n_D^{25} = 1.4513$. The yield was 9 g. (82%).

Carbobenzyloxyglycyl-DL-phenylalanine.[381] A solution of 1.04 g. of carbobenzyloxyglycine and 1.48 g. of diethyl α-ethoxy-β-carbethoxyvinyl phosphate in 2 ml. of acetone was heated at 70° for 1 hour. The reaction mixture was cooled, diluted with 2 ml. of benzene, and dropped slowly into a solution of 0.82 g. of DL-phenylalanine and 0.2 g. of sodium hydroxide in 2 ml. of water containing phenolphthalein. The solution was kept basic by the addition of 2N sodium hydroxide as needed. The benzene layer was separated, the aqueous layer acidified with concentrated hydrochloric acid, and the precipitated carbobenzyloxy peptide recrystallized from water. The yield was 1.05 g. (61%) of material, m.p. 160°.

α-ACYLAMINOACYL DICHLOROPHOSPHATES

The reaction of two moles of carbobenzyloxyglycine with phenyl dichlorophosphate in the presence of a tertiary base gave bis-carbobenzyloxyglycyl phenyl phosphate.[48] This mixed anhydride reacts with sodium glycinate to give carbobenzyloxyglycylglycine in the low yield of 30%, which was interpreted as an indication of rapid disproportionation.

Carbobenzyloxyglycine, when treated with N-ethylpiperidine and phosphorus oxychloride in tetrahydrofuran, failed to react with sodium glycinate.[48] A reinvestigation of the use of phosphorus oxychloride with non-aqueous solvents, employing amino acid esters rather than free amino acids, showed that peptide synthesis was possible. Fifteen peptide intermediates were prepared in yields of 62% to 95%.[130] Of special interest is the preparation of carbobenzyloxy-L-hydroxyprolyl-L-tryptophan methyl ester. While this compound was obtained as a glass in 75% yield, saponification and hydrogenolysis gave crystalline L-hydroxyprolyl-L-tryptophan. Apparently sulfhydryl groups are oxidized with phosphorus oxychloride in the presence of a tertiary amine, thus preventing a compound like methyl cysteinate from being satisfactorily acylated by α-aminoacyl dichlorophosphates.

The reaction of phosphorus oxychloride with a mixture of the α-acylamino acid and the α-amino acid ester proceeds via the α-acylaminoacyl

procedure, and the standard procedure.[410] The course of the reactions using tetraethyl pyrophosphate (CXI) is indicated in the accompanying equations. Similar reactions occur when halophosphites are used in place of the pyrophosphate.[42, 382]

Anhydride Procedure

$$R_1CONHCHR_2CO_2H + (C_2H_5O)_2POP(OC_2H_5)_2$$
$$CXI$$

$$R_1CONHCHR_2CO_2P(OC_2H_5)_2 + HOP(OC_2H_5)_2$$

$$\downarrow H_2NCHR_3CO_2C_4H_9$$

$$R_1CONHCHR_2CONHCHR_3CO_2C_4H_9 + HOP(OC_2H_5)_2$$
$$CXII$$

Amide Procedure

$$H_2NCHR_3CO_2C_4H_9 + CXI \rightarrow (C_2H_5O)_2PNHCHR_3CO_2C_4H_9 + HOP(OC_2H_5)_2$$

$$\downarrow R_1CONHCHR_2CO_2H$$

$$CXII + HOP(OC_2H_5)_2$$

Standard Procedure

$$R_1CONHCHR_2CO_2H + H_2NCHR_3CO_2C_4H_9 + CXI \rightarrow CXII + HOP(OC_2H_5)_2$$
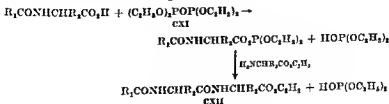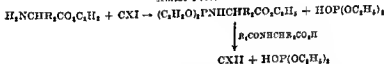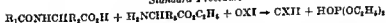
These reactions indicate that disproportionation of mixed phosphite anhydrides, unlike most other mixed anhydrides, will not necessarily lower the yields of products. Disproportionation merely produces more tetraalkyl pyrophosphate which can react with either the amine component or the acid component to give additional active intermediate.

The amide procedure, although very useful, is not within the scope of this chapter. In the standard procedure, the reagent is added to a mixture of the amine and acid. Since the addition of phosphorus trichloride to an acid and an amine leads to a reaction, proceeding by way of a phosphorazo compound and not via an acid chloride,[413] it is believed that the standard procedure also proceeds primarily via the phosphite amine and not via the mixed anhydride. However, in the preparation of intermediates for the synthesis of oxytocin, the addition of diethyl chlorophosphite to a pyridine solution of carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosine and methyl L-isoleucinate according to the general procedure used in the phosphorazo peptide synthesis[414] led to a partially racemized product. This could be avoided by allowing the chlorophosphite to

---

[410] Grimmel, Guenther, and Morgan, *J. Am. Chem. Soc.*, **68**, 539 (1946).

[414] Goldschmidt and Lautenschlager, *Ann.*, **580**, 68 (1953).

$$R_1CONHCHR_2CO_2H + ClP(OC_2H_5)_2 + (C_2H_5)_3N \rightarrow$$
$$R_1CONHCHR_2CO_2P(OC_2H_5)_2 + (C_2H_5)_3NHCl$$

$$2R_1CONHCHR_2CO_2H + Cl_2POC_2H_5 + 2(C_2H_5)_3N \rightarrow$$
$$(R_1CONHCHR_2CO_2)_2POC_2H_5 + 2(C_2H_5)_3NHCl$$

$$R_1CONHCHR_2CO_2H + (C_2H_5O)_2POP(OC_2H_5)_2 \rightarrow$$
$$R_1CONHCHR_2CO_2P(OC_2H_5)_2 + HOP(OC_2H_5)_2$$
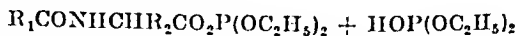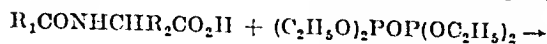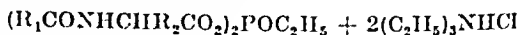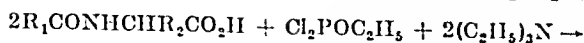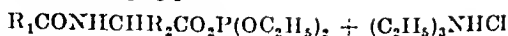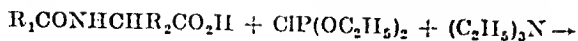
These phosphite mixed anhydrides react with amines to form amides.

$$R_1CONHCHR_2CO_2P(OC_2H_5)_2 + H_2NCHR_3CO_2C_2H_5 \rightarrow$$
$$R_1CONHCHR_2CONHCHR_3CO_2C_2H_5 + HOP(OC_2H_5)_2$$
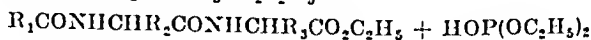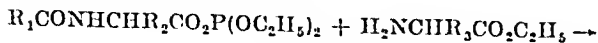
The method was developed by Young[399-408] and Anderson[42, 409-411] and co-workers.

The structure of the intermediate phosphorus compounds has not been rigorously established. None of the mixed α-acylaminoacyl phosphite anhydrides has been obtained in crystalline form, and attempted distillation of even the simpler mixed anhydrides leads to decomposition.[42] However, similar anhydrides from organic acids such as butyric acid and tetraethyl pyrophosphite have been distilled.[412] The molecular refractivity for butyric acid diethyl phosphite was 49.3 as compared with a theoretical value of 49.6.[400] Although the proposed structures depend for the most part on analogies, there is little doubt about their correctness.

Mechanism

The phosphite method of peptide synthesis differs from most other methods in that the reagent will react with either the carboxylic acid or the amine function to give a useful reactive intermediate. The nature of the intermediate depends upon the order of mixing the reactants, and the methods have been referred to as the anhydride procedure, the amide

[399] Young, U.S. pat. 2,017,793 (to American Cyanamid) [C.A., 48, 1438 (1954)].

[400] Young, U.S. pat. 2,059,747 (to American Cyanamid) [C.A., 48, 12794 (1954)].

[401] Young, Ger. pat. 900,223 (to American Cyanamid) [Chem. Zentr., 126, 2302 (1955)].

[402] Young, Brit. pat. 717,427 (to American Cyanamid) [Chem. Zentr., 126, 11734 (1955)].

[403] Young and Barbaro, U.S. pat. 2,708,607 (to American Cyanamid) [C.A., 50, 5733 (1956)].

[404] Young, Can. pat. 534,789 (to American Cyanamid) (1950).

[405] Young and Barbaro, Can. pat. 534,793 (to American Cyanamid) (1956).

[406] Young, Wood, Joyce, and Anderson, J. Am. Chem. Soc., 78, 2126 (1956).

[407] Brit. pat. 714,018 (to American Cyanamid) [C.A., 50, 1899e (1956)].

[408] Fr. pat. 1,072,309 (to American Cyanamid) [Chem. Zentr., 128, 14211 (1957)].

[409] Anderson, U.S. pat. 2,091,010 (to American Cyanamid) [C.A., 49, 11709f (1955)].

[410] Anderson, Blodinger, and Welcher, J. Am. Chem. Soc., 74, 5309 (1952).

[411] Anderson, Welcher, and Young, J. Am. Chem. Soc., 73, 501 (1951).

[412] Arbuzov and Alimov, Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk, 1951, 409 [C.A., 49, 159i (1955)].

Diethyl benzoyl phosphite and ethanol give benzoic acid and triethyl phosphate.[412] Whether a reaction of this type will interfere with the acylation of a serine ester by an acylaminoacyl phosphite is not known.

The phosphite mixed anhydrides are relatively stable to disproportionation. The mixed anhydride formed between o-phenylene chlorophosphite and phthaloylglycine deposited only 20% of the symmetrical phthaloylglycine anhydride on standing for 2 days at 30°.[42]

No racemization was observed when carbobenzyloxy- or phthaloyl-amino acids were used.[419] When the acid component was an acyldipeptide, the extent of racemization depended upon the reaction conditions. The anhydride method resulted in more racemization than the amide method. Final addition of tetraethyl pyrophosphite gave results essentially the same as those obtained by the amide procedure, thus substantiating the view that both proceed via the amide. Substitution of ethyl glycinate hydrochloride and triethylamine for ethyl glycinate as the amine component increased racemization with each of the three methods, but the increase was most pronounced with the anhydride procedure. The use of hydrocarbon solvents such as benzene or toluene tends to minimize racemization, presumably by removing triethylammonium chloride from solution. In these solvents no racemization was observed when carbobenzyloxyglycyl-L-leucyl-o-phenylene phosphite or carbobenzyloxyglycyl-L-phenylalanyl-o-phenylene phosphite was coupled with glycine ester.[42, 299] Racemization does not occur in the absence of the anhydride-forming reagent. On the basis of these facts it has been suggested that racemization is due to the formation of an oxazolonium salt.[406]

Experimental Conditions

Preparation of the Phosphite. Diethyl chlorophosphite, which is frequently employed, is readily prepared in about 50% yield from phosphorus trichloride, ethanol, and diethylanilines in ether.[419] o-Phenylene chlorophosphite, which can be prepared from catechol and phosphorus trichloride in 94% yield, offers some advantages in stability.[292, 420, 421] It has been reported[88] that diethyl chlorophosphite will sometimes suddenly decompose on vacuum distillation with liberation of an inflammable gaseous by-product whereas o-phenylene chlorophosphite has never given any evidence of decomposition. Ethyl dichlorophosphite is prepared in 40–50% yields from ethanol and phosphorus trichloride.[422]

[419] Cook, Ilett, Saunders, Stacey, Watson, Wilding, and Woodcock, J Chem Soc. 1949, 2921.

[420] Anschutz, Broeker, Neher, and Ohnheuser, Ber., 79, 222 (1943).

[421] Crofts, Markes, and Ryden, J Chem Soc, 1958, 4250

[422] Menschutkin, Ann., 139, 343 (1866)

react first with the isoleucine ester, using the amide procedure.[392, 411] These results suggest that the standard procedure proceeds, at least in part, via the mixed anhydride and not exclusively via the phosphite amide.

The reaction of an acid and an amine in the presence of dihalophosphite such as ethyl dichlorophosphite proceeds as shown in the accompanying

$$2R_1CONHCHR_2CO_2H + 2H_2NCHR_3CO_2C_2H_5 + C_2H_5OPCl_2 \rightarrow$$
$$2R_1CONHCHR_2CONHCHR_3CO_2C_2H_5 + 2HCl + C_2H_5OP(OH)_2$$
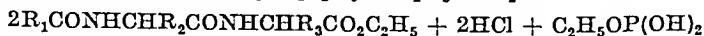
equation.[403, 407, 408] The nature of the intermediate has not been established, but three possibilities have been suggested, namely structures CXIII, CXIV, and CXV. It is probable that the order of addition is the
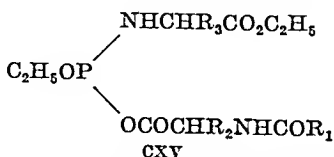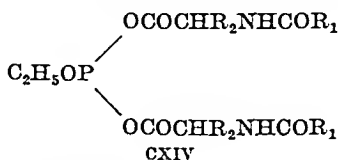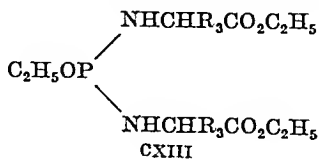
principal factor determining the particular intermediate obtained and that appreciable amounts of the mixed anhydride CXIV can be obtained only if the amine component is added last.

Scope and Limitations

Phosphite mixed anhydrides have been used to prepare peptides of glycine, DL-alanine, DL-valine, L-leucine, L-phenylalanine, L-tyrosine, and L-lysine. The method should be as applicable as the alkyl carbonate mixed anhydride procedure. Lower than average yields may be anticipated with L-serine, L-threonine, L-asparagine, and L-glutamine derivatives. However, merely reversing the order of addition of the reactants so that the phosphite amide is formed rather than the mixed anhydride should obviate this difficulty. L-Asparagine peptides have been prepared by the amide procedure.[66, 415, 416] This method has also been used to synthesize a peptide of L-arginine[23, 406] and key intermediates of oxytocin[417, 418] and arginine vasopressin.[86]

[415] Miller, Neidle, and Waelsch, *Arch. Biochem. Biophys.*, 56, 11 (1955).

[416] Miller and Waelsch, *Arch. Biochem. Biophys.*, 35, 176 (1952).

[417] du Vigneaud, Ressler, Swan, Roberts, and Katsoyannis, *J. Am. Chem. Soc.*, 76, 3115 (1954).

[418] du Vigneaud, Ressler, Swan, Roberts, Katsoyannis, and Gordon, *J. Am. Chem. Soc.*, 75, 4879 (1953).

preparation of the mixed anhydride by the pyrophosphite procedure, the α-acylamino acid or acylpeptide is warmed with the tetraethyl pyrophosphite for 2 minutes, and the amine to be acylated is then added.[410] Tetrahydrofuran has been suggested as a solvent for peptide synthesis with tetraethyl pyrophosphite.[439]

Formation of the Amide Bond. The mixed anhydride in solution reacts with an α-amino acid ester or peptide ester. The α-amino acid ester hydrochloride may be used and a mole of triethylamine added to liberate the amine, but better results are usually obtained if the base is used directly. The solution may be warmed for 15 minutes on the steam bath,[42, 406] or allowed to stand for 12 hours at room temperature[399] to complete the reaction. Heating the reaction mixture gives better yields,[410] but room temperature is preferable if ammonium salts are present.[406] Reactions carried out in water-immiscible solvents are worked up by washing with water, aqueous sodium bicarbonate, and again with water. In many cases an acid wash would also be advisable. After drying, the solvent is removed to give the α-acylpeptide ester Yields generally range from 50% to 92%. With water-miscible solvents the product may usually be precipitated by addition of water. The addition of 5% aqueous sodium bicarbonate to dissolve unreacted α-acylamino acid frequently causes only products to crystallize.[410] The crude products are recrystallized from aqueous ethanol, ethyl acetate-hexane, or other suitable solvents.

Experimental Procedures

Ethyl Carbobenzyloxyglycyl-L-phenylalanylglycinate (Use of a Dialkyl Chlorophosphite).[43] To a solution of 1.789 g. of carbobenzyl-oxyglycyl-L-phenylalanine in 50 ml. of benzene containing 0.6 g. of triethylamine was added 0.83 g. of o-phenylene chlorophosphite. The solution was filtered and the filtrate heated to boiling for 15 minutes with 0.5 g. of distilled ethyl glycinate. The solution was cooled and 25 ml. of ethyl acetate added to facilitate separation of two phases. The organic layer was washed with water, aqueous sodium bicarbonate, and water. Removal of the solvent left an oil which rapidly crystallized upon the addition of 10 ml. of anhydrous ethyl ether. The product weighed 2.03 g. (92.5%), m.p. 115–118°, $[\alpha]_D^{25}$ −11.5° (c = 2%, ethanol) Recrystallization from 20 ml. of ethyl acetate-petroleum ether gave 1.85 g. (89%) of product, m.p. 116–118°, $[\alpha]_D^{25}$ −12.0°.

Methyl Carbobenzyloxyglycyl-L-leucyl-L-leucinate (Use of an Alkyl Dichlorophosphite).[406] To a solution of 3.2 g. (0.01 mole) of carbobenzyloxyglycyl-L-leucine in 30 ml. of benzene containing 1.09

410 Brenner and Rufenacht, *Helv. Chim. Acta,* 37, 209 (1954)

and tetraethyl pyrophosphite is prepared from diethyl phosphite and ethyl chlorophosphite in benzene in the presence of triethylamine.[410, 423-426] A similar method of synthesis is used for the preparation of diethyl ethylenepyrophosphite.[427] Diethylene pyrophosphite has been prepared from ethylene chlorophosphite and water in the presence of triethylamine.[427] The refractive index has been used as a criterion of purity of tetraethyl pyrophosphite.[410] Bis-*o*-phenylene pyrophosphite may be prepared in 87% yield from *o*-phenylene chlorophosphite and water.[421]

Preparation of the α-Acylaminoacyl Phosphite. When a dialkyl chlorophosphite is employed to prepare the mixed anhydride, it is added to the solution of the α-acylamino acid in an inert solvent in the presence of a base such as triethylamine. The silver salt of carbobenzyloxyglycine has been used in chloroform to prepare the mixed anhydride with diethyl chlorophosphite, but the over-all yield of carbobenzyloxyglycine anilide was only 22% as compared with an 88% yield when the triethylammonium salt in benzene was used.[399] The mixed anhydride is formed rapidly at the usual reaction temperature of 15° to 25°. Young[399] reports that chlorinated hydrocarbons, aliphatic ethers, and dioxane are useful solvents, although aromatic hydrocarbons such as benzene and toluene are preferred.[42] Aliphatic ketones and esters give less satisfactory results. The presence of thiophene in toluene used as a solvent is claimed to lower the yields when the phosphite amide procedure is used.[66] It is not known whether this observation can be extrapolated to the mixed anhydride procedure. In any event, this observation is sufficiently unusual to warrant confirmation. If true, poor results might be obtained with cysteine and methionine peptides.

The triethylamine hydrochloride, formed in quantitative yield, is removed by filtration to give a solution of the mixed anhydride which is normally used without isolation.

The use of dihalophosphite, preferably ethyl dichlorophosphite, involves no change in experimental procedure except that 1 mole of dichlorophosphite is used for 2 moles of acid and 2 moles of amine.[403, 406-408]

Tetraethyl pyrophosphite may be employed in excess without added solvent.[410] Trialkyl phosphites have been recommended as acid acceptors with alkyl dichlorophosphites or tetraalkyl pyrophosphites.[428] In the

[423] Young, Blodinger, and Welcher, U.S. pat. 2,660,603 (to American Cyanamid) [*C.A.*, 48, 12167f (1954)].

[424] Young, Blodinger, and Welcher, Can. pat. 515,171 (to American Cyanamid).

[425] Maclaren, *Proc. Intern. Wool Textile Conference*, Australia, 1955, C, 168; Discussion, p. 480 (Pub. 1956).

[426] Maclaren, *Angew. Chem.*, 68, 218 (1956).

[427] Anderson, U.S. pat. 2,722,539 (to American Cyanamid) [*C.A.*, 50, 3498 (1956)].

[428] Anderson and Young, U.S. pat. 2,722,526 (to American Cyanamid) [*C.A.*, 50, 4237h (1956)].

given slightly better yields than the anhydride method in the two cases where the same compound was prepared by both procedures.

TABULAR SURVEY

In the following tables are listed peptide intermediates prepared by the use of mixed anhydrides. Each table, which deals with a single mixed anhydride, is arranged according to the increasing number of amino acid residues in the product. Peptides with the same number of residues are arranged according to increasing number of residues in the acylating species. Further subdivision depends upon the particular amino acid which forms the anhydride, aliphatic, aromatic, acidic, basic, and unnatural amino acids appear in that order.

A dash in the solvent or yield column indicates that the solvent or yield was not reported.

The literature was surveyed through the March 25, 1959, issue of *Chemical Abstracts*. Abstracts were relied upon only in those few cases in which it was impossible to secure a copy or photostat of the original. Those peptide intermediates appearing in the patent literature which most probably have never been made have been omitted from the tables.

The amino acid residues, —HNCHRCO—, are abbreviated according to the system developed by Erlanger and Brand[26] in which the first three letters of the name represent the particular residue. For those not familiar with peptide chemistry, abbreviations are listed below.

Amine Protecting Groups

Cbzo	$C_6H_5CH_2OCO—$	Carbobenzyloxy or benzyloxycarbonyl
4-NO₂Cbzo	$4-O_2NC_6H_4CH_2OCO—$	p-Nitrocarbobenzyloxy
Phth		Phthalyl
Tos	$4\ CH_3C_6H_4SO_2—$	Tosyl or p toluene sulfonyl
Tri	$(C_6H_5)_3C—$	Trityl or triphenylmethyl

Amino Acids

Ala	$—HNCH(CH_3)CO—$	Alanyl
H Ala.OH	$H_2NCH(CH_3)CO_2H$	Alanine
H β.Ala.OH	$H_2NCH_2CH_2CO_2H$	β Alanine
H.Asp OH	$H_2NCH(CH_2CO_2CH_3)CO_2H$	β Methyl aspartate
H.Asp OCH₃	$H_2NCH(CH_2CO_2H)CO_2CH_3$	α Methyl aspartate

[26] Erlanger and Brand, *J Am Chem Soc*, 73, 3516 (1950).

(0.01 mole) of triethylamine was added 0.74 g. (0.005 mole) of ethyl dichlorophosphite in 10 ml. of benzene. The amine hydrochloride was removed by filtration, 1.5 g. (0.01 mole) of distilled methyl L-leucinate added to the filtrate, and the solution held under reflux for 15 minutes. The cooled reaction mixture was washed with 10 ml. of water and 15 ml. of saturated aqueous sodium bicarbonate. The benzene solution was dried and concentrated under reduced pressure and the residue recrystallized from ethyl acetate-petroleum ether to give a 60% yield of product, m.p. 133–134°; $[\alpha]_D^{25}$ −47.4° ($c = 2\%$, methanol).

α-ACYLAMINOACYL ARSENITES

The properties of diethyl chloroarsenite are very similar to those of diethyl chlorophosphite. The reagent is readily prepared from arsenic trichloride and ethanol[430] and is relatively stable. The arsenite mixed anhydride is prepared from the α-acylamino acid and diethyl chloroarsenite in an inert solvent such as toluene in the presence of triethylamine.[431, 432] The triethylamine hydrochloride is removed by filtration, and the mixed anhydride in solution is used directly for reaction with an amino acid ester. Heating under reflux for 1 hour completes the reaction.

$$C_6H_5CH_2OCONHCH_2CO_2H + ClAs(OC_2H_5)_2 + (C_2H_5)_3N \rightarrow$$
$$C_6H_5CH_2OCONHCH_2COOAs(OC_2H_5)_2 + (C_2H_5)_3NHCl$$
$$\text{CXVI}$$

$$\text{CXVI} + H_2NCHCO_2C_2H_5 \rightarrow$$
$$\quad\quad\quad\quad\quad | $$
$$\quad\quad\quad\quad CH_2C_6H_5$$

$$C_6H_5CH_2OCONHCH_2CONHCHCO_2C_2H_5 + HOAs(OC_2H_5)_2$$
$$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad | $$
$$\quad\quad\quad\quad\quad\quad\quad\quad\quad CH_2C_6H_5$$
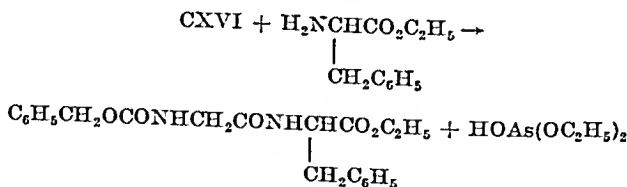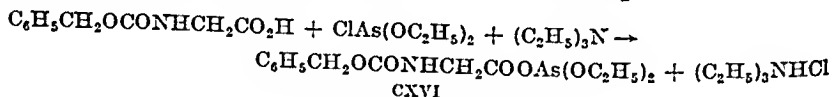
This method has been used to prepare ethyl carbobenzyloxyglycyl-DL-phenylalaninate (52%), ethyl carbobenzyloxy-DL-alanyl-DL-phenyl-alaninate (60%), ethyl carbobenzyloxy-L-leucyl-DL-phenylalaninate (74%), and ethyl carbobenzyloxyglycylglycyl-DL-phenylalaninate (30%).

The diethyl chloroarsenite may also be initially added to the amino acid or peptide ester to form the arsenite amide.[433] The amide is then allowed to react with an α-acylamino acid.[434, 435] This procedure has

[430] McKenzie and Wood, J. Chem. Soc., 117, 406 (1920).
[431] Vaughan, U.S. pat. 2,659,745 (to American Cyanamid) [C.A., 48, 13709h (1954)].
[432] Vaughan, Can. pat. 537,983 (to American Cyanamid) (1957).
[433] Vaughan, U.S. pat. 2,631,158 (to American Cyanamid). [C.A., 49, 1792i (1955)].
[434] Vaughan, J. Am. Chem. Soc., 73, 1389 (1951).
[435] Vaughan, U.S. pat. 2,617,795 (to American Cyanamid) [C.A., 48, 1438i (1954)].

Amino Acids—Continued

H.Tyr OH	p-HOC$_6$H$_4$CH$_2$CH(NH$_2$)CO$_2$H	Tyrosine
H.Val.OH	(CH$_3$)$_2$CHCH(NH$_2$)CO$_2$H	Valine

Optical Configuration

H.L.Ala OH	L-H$_3$NCH(CH$_3$)CO$_2$H	L-Alanine
H D Phe.OH	D-H$_3$NCH(CH$_2$C$_6$H$_5$)CO$_2$H	D-Phenylalanine
H.Leu OH	(CH$_3$)$_2$CHCH$_2$CH(NH$_2$)CO$_2$H	Configuration not stated in literature

Amino Acids—Continued

NH_2		
H.Asp.OH	$H_2NCH(CH_2CONH_2)CO_2H$	Asparagine
OH		
H.Asp.NH$_2$	$H_2NCH(CH_2CO_2H)CONH_2$	Isoasparagine
	NH	
H.NO$_2$.Arg.OH	$O_2NNHCNHCH_2CH_2CH_2CH(NH_2)CO_2H$	Nitroarginine
H.Cys.OH	$HSCH_2CH(NH_2)CO_2H$	Cysteine
H.S.Bz.Cys.OH	$C_6H_5CH_2SCH_2CH(NH_2)CO_2H$	S-Benzylcysteine
NH_2		
H.Glu.OH	$H_2NCH(CH_2CH_2CONH_2)CO_2H$	Glutamine
OH		
H.Glu.NH$_2$	$H_2NCH(CH_2CH_2CO_2H)CONH_2$	Isoglutamine
H.Gly.OH	$H_2NCH_2CO_2H$	Glycine

H.His.OH   Histidine

H.*im*.C$_6$H$_5$CH$_2$··   Iminobenzylhistidine
His.OH*

H.Ileu.OH	$(CH_3)(C_2H_5)CHCH(NH_2)CO_2H$	Isoleucine
H.Leu.OH	$(CH_3)_2CHCH_2CH(NH_2)CO_2H$	Leucine
Cbzo		
H.Lys.OH	$C_6H_5CH_2OCONH(CH_2)_4CH(NH_2)CO_2H$	ϵ-Carbobenzyloxylysine
H.Met.OH	$CH_3SCH_2CH_2CH(NH_2)CO_2H$	Methionine
H.Nleu.OH	$CH_3CH_2CH_2CH_2CH(NH_2)CO_2H$	Norleucine
H.Nval.OH	$CH_3CH_2CH_2CH(NH_2)CO_2H$	Norvaline

H.HO.Pro.OH   Hydroxyproline

H.Phe.OH	$C_6H_5CH_2CH(NH_2)CO_2H$	Phenylalanine

H.Pro.OH   Proline

H.Ser.OH	$HOCH_2CH(NH_2)CO_2H$	Serine
H.Thr.OH	$CH_3CHOHCH(NH_2)CO_2H$	Threonine

H.Try.OH   Tryptophan

Amino Acids—Continued

H.Tyr.OH	p HOC$_6$H$_4$CH$_2$CH(NH$_2$)CO$_2$H	Tyrosine
H.Val.OH	(CH$_3$)$_2$CHCH(NH$_2$)CO$_2$H	Valine

Optical Configuration

H.L.Ala.OH	L-H$_3$NCH(CH$_3$)CO$_2$H	L-Alanine
H.D.Phe.OH	D-H$_3$NCH(CH$_2$C$_6$H$_5$)CO$_2$H	D-Phenylalanine
H.Leu OH	(CH$_3$)$_2$CHCH$_2$CH(NH$_2$)CO$_2$H	Configuration not stated in literature

TABLE I

ANHYDRIDE FORMATION WITH PHOSGENE

Acid	Amine	Solvent	Yield, %	Reference
o-HOC$_6$H$_4$CO.L.Phe.OH	H.Gly.OCH$_3$	Toluene-THF*	50	53

* THF is tetrahydrofuran.

TABLE II

ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
HCO.Gly.OH	p-H$_2$NC$_6$H$_4$CO$_2$H	Acetone	47	13
CH$_3$CO.Gly.OH	p-H$_2$NC$_6$H$_4$CO$_2$H	Dioxane	52	13
	p-H$_2$NC$_6$H$_4$CO$_2$C$_2$H$_5$	Chloroform	52	13
Cbzo.Gly.OH	H.Gly.SC$_2$H$_5$	THF*	73	37
	H.Leu.OCH$_3$	Chloroform	89	314
	H.L.Leu.OC$_2$H$_5$	Toluene	—	437
	H.L.Leu.SC$_6$H$_5$	THF	70	37
	H.S.Bz.L.Cys.OC$_2$H$_5$	Chloroform	54	348
	H.S.Bz.L.Cys.OCH$_2$C$_6$H$_5$	Chloroform	53	348
	H.L.Pro.OH	—	20	59
	H.DL.Pro.OH	—	18	59
	H.DL.Ser.OH	DMF†	88	69
	H.DL.Ser.OCH$_2$C$_6$H$_5$	DMF	72	69
	H.L.Asp(OCH$_2$C$_6$H$_5$)$_2$ NH$_2$	Dioxane	79	415
	H.L.Asp.OH	Dioxane	—	66
	H.L.Glu(OC$_2$H$_5$)$_2$	Chloroform	76	317
	H.L.Lys.OCu/2	THF	50	61

H.NO₂.L.Arg.OCH₃	Dioxane	54‡	438, 439
H.DL.Thr.OC₂H₅	Toluene	—	440
H.L.Try.OC₂H₅	Chloroform	70	441
[SCl₂.CH₃CH₂]CO₂H₅	—	61	442
H.L.Glu(OCH₃)₂	Chloroform	51	317
H.L.Glu(OC₂H₅)₂	Chloroform	57	317
H.L.Glu(OCH₃)₂C₂H₅	Chloroform	72 crude	317
H.Gly.OC₂H₅	Toluene	43	443, 444
H.Gly.OH	Chloroform	62	125, 152
H.Gly.OC₂H₅	Chloroform	70	54, 125
H.S.Bz.L.Cys.OC₂H₅	Dioxane	01	348
H.DL.Ser.OH	Dioxane	02	445
H.DL.Ser.OCH₃			

p-NO₂C₆H₄.CO.Gly.OH			
C₆H₅.CH₂.CO.Gly.OH			
Phth Gly.OH			

$$\begin{array}{c} NH_2 \\ | \\ H.L.Asp.OH \end{array}$$

	Dioxane	72	60
H.L.Glu(OCH₃)₂	Chloroform	70 crude	317
H.L.Glu(OC₂H₅)₂	Chloroform	77 crude	317
H.L.Glu(OC₂H₅)C₂H₅	Chloroform	80 crude	317
H.m.Glu.OH	Dioxane	72	64
p-H₂.NC₆H₄.CO₂H	Dioxane	65	13

Note: References 437 to 458 are on pp. 353-355.

* THF is tetrahydrofuran.

† DMF is dimethylformamide.

‡ This is the yield after saponification.

TABLE II—*Continued*

ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Phth.Gly.OH (*continued*)	(L) H₂C——CHCO₂CH₃ / NH / S—C—CH₃ / H₃C (thiazolidine structure)	Methylene dichloride	41	32
(C₆H₅CH₂)₂.Gly.OH	H.dl.Val.OC₂H₅	Chloroform	92	446, 447
	D.dl.Ser.OC₂H₅	Chloroform	95	446, 447
	H.Gly.OC₂H₅	Chloroform	98	446, 447
	H.l.Glu(OC₂H₅)₂	Chloroform	90	446, 447
	H.dl.Try.OCH₃	Chloroform	77	446, 447
Tri.Gly.OH	H.Gly.OC₂H₅	Chloroform	63–90	9, 10, 448, 449
	H.dl.Met.OH	Benzene	—	9, 10
	H.im.C₆H₅CH₂.l.His.OCH₂C₆H₅	THF	60	227
	H.im.C₆H₅CH₂.l.His.OCH₃	—	—	450
	Cbzo │ H.l.Lys.OCH₃	THF	88	45
	H.dl.Try.OOH	Chloroform	90	10, 448, 449
Stearoylglycine	H.Gly.OH	THF	75–80	451
	H.β.Ala.OH	THF	75–80	451

$$\overset{\mathrm{NH_2}}{\underset{\mathrm{H \cdot L \cdot Asp \cdot OH}}{|}}$$

			70-75	80-90 crude	451
Cbzo·L·Ala·OH	H₂NCH₂CH₂SO₂H	THF		80	452
Cbzo·L·Ala·OH	H·Gly·OC₂H₅	—		67	37
	H·Gly·OC₄H₉·NO₂-p	THF		70	37
Cbzo·L·Ala·OH	H·Gly·SC₂H₅	THF		80§	451
Cbzo·DL·Ala·OH	H·L·Ala·NH·C₁₆H₃₃-n	THF		64	453
Cbzo·L·Ala·OH	H·β·Ala·OH	THF		51	454-456
Cbzo·L·Ser·OH	H·L·Ser·OCH₃	Chloroform			

$$\overset{\mathrm{OH}}{\underset{\mathrm{H \cdot L \cdot Glu \cdot OCH_2C_6H_5}}{|}}$$

	H·L·Glu·OCH₂C₆H₅	Dioxane	45‖		97
	H₂SO₄·L·Arg·OCH₃	Dioxane	70‖		90
Cbzo·DL·Ala·OH		Dioxane	60‡		438, 439
	n-C₄H₉·CH·OH·CH(NH₂)·CO₂H	THF	40‡		457

$$\overset{\mathrm{NH_2}}{\underset{\mathrm{H \cdot L \cdot Asp \cdot OH}}{|}}$$

Phth·L·Ala·OH		Dioxane	—		60

$$\overset{\mathrm{NH_2}}{\underset{\mathrm{H \cdot L \cdot Asp \cdot OH}}{|}}$$

Phth·DL·Ala·OH		Dioxane	50		60

Note: References 437 to 538 are on pp. 353-355.

‡ This is the yield after saponification.
† This is the yield after hydrogenolysis.
‖ Other optical isomers were prepared.

TABLE II—*Continued*

ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Phth.Gly.OH (*continued*)	(L) H_2C——$CHCO_2CH_3$, NH, $\underset{H_3C}{\overset{}{}}C\underset{CH_3}{\overset{}{}}$, S	Methylene dichloride	41	32
$(C_6H_5CH_2)_2$.Gly.OH	H.DL.Val.OC_2H_5	Chloroform	92	446, 447
	D.DL.Ser.OC_2H_5	Chloroform	95	446, 447
	H.Gly.OC_2H_5	Chloroform	98	446, 447
	H.L.Glu(OC_2H_5)$_2$	Chloroform	90	446, 447
	H.DL.Try.OCH_3	Chloroform	77	446, 447
Tri.Gly.OH	H.Gly.OC_2H_5	Chloroform	63–90	9, 10, 448, 449
	H.DL.Met.OH	Benzene	—	9, 10
	H.*im*.$C_6H_5CH_2$.L.His.$OCH_2C_6H_5$	THF	60	227
	H.*im*.$C_6H_5CH_2$.L.His.OCH_3	—	—	450
	Cbzo | H.L.Lys.OCH_3	THF	88	45
	H.DL.Try.OCH_3	Chloroform	90	10, 448, 449
Stearoylglycine	H.Gly.OH	THF	75–80	451
	H.β.Ala.OH	THF	75–80	451

$$NH_2$$
H.Asp.OH

			80-90 crude	70-75	
Cbzo.L.Ala.OH	$H_2.NCH_2CH_2SO_3H$	THF	80		451
Cbzo.D.Ala.OH	H.Gly.OC$_3$H$_5$	—	07		452
	H.Gly.OC$_2$H$_5$NO$_2$-p	THF	70		37
	H.Gly.SC$_2$H$_5$	THF	80§		37
Cbzo.L.Ala.OH	H.Ala.NH$_2$H$_{10}$..*	THF	04		451
Cbzo.DL.Ala.OH	H.Ser.OCH$_3$	THF	51		453
Cbzo.L.Ala.OH		Chloroform			454-456

OH
H.L.Glu.OH

			80-90 crude	70-75	
	H.L.Glu.OH	Dioxane	45‡		07
	H.L.Glu(OCH$_2$C$_6$H$_5$)$_2$	Dioxane	70‖		90
Cbzo.DL.Ala.OH	H$_2$SO$_3$..L.Arg.OCH$_3$	Dioxane	66‡	438, 439	
	i-C$_3$H$_7$.CHOHCH$_2$CH$_2$.CO$_2$H	THF	40§		457

$$NH_2$$
H.A.Asp.OH

			80-90 crude	
19.th.L.Ala.OH	H.A.Asp.OH	Dioxane	—	00

$$NH_2$$
H.L.Asp.OH

			80-90 crude	
19.th.DL.Ala.OH	H.L.Asp.OH	Dioxane	50	65

Note: References 437 to 538 are on pp. 353-355.

‡ This is the yield after saponification.

§ This is the yield after hydrogenolysis.

‖ Other optical isomers were prepared.

TABLE II—*Continued*

ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
$(C_6H_5CH_2)_2$.DL.Ala.OH	H.DL.Try.OCH$_3$	Chloroform	90	446, 447
	DL-C$_2$H$_5$CH(NH$_2$)CO$_2$C$_2$H$_5$	Chloroform	80	446, 447
Tri.DL.Ala.OH	H.Gly.OC$_2$H$_5$	Chloroform	80–88	10, 448, 449
	H.DL.Ser.OC$_2$H$_5$	Chloroform	68	10, 448, 449
	H.DL.Try.OCH$_3$	Chloroform	90	10, 448, 449
Stearoylalanine	H.Ala.OH	THF	—	451
Cbzo.β.Ala.OH	H.DL.Ala.OH	THF	87	453
	H.β.Ala.NHC$_{18}$H$_{37}$-n	THF	—	451
	H.DL.Ser.OH	DMF	48	122
	H.L.Phe.OC$_2$H$_5$	Methylene dichloride	100	458
	H.L.Tyr.OC$_2$H$_5$	Methylene dichloride	96	458
	DL-CH$_3$CH(NH$_2$)CH$_2$CO$_2$H	THF	96	453
	DL-i-C$_3$H$_7$.CH(NH$_2$)CH$_2$CO$_2$H	THF	91	453
	DL-CH$_3$SCH$_2$CH(NH$_2$)CH$_2$CO$_2$H	THF	28	453
Stearoyl-β-alanine	H.Gly.OH	THF	75	451
	H.β.Ala.OH	THF	71	451
	H$_2$NCH$_2$CH$_2$SO$_3$H	THF	78	451
Cbzo.DL.Ser.OH	H.Gly.OCH$_2$C$_6$H$_5$	DMF	50	69
	H.L.Leu.OCH$_2$C$_6$H$_5$	Dioxane	55¶	70
Cbzo.L.Pro.OH	H.Gly.OC$_2$H$_5$	THF	88	459
Cbzo.DL.Pro.OH	H.Gly.OC$_2$H$_5$	Chloroform	94 crude	59
Cbzo.L.Pro.OH	H.Gly.OC$_2$H$_5$	Chloroform	98 crude	59

Cbzo.Pro.OH	H.L.Val.OCH₃	THF	81	45
HCO.DL.Val.OH	H.NO₂.L.Arg.OCH₃	Dioxane	00‡	438, 439
Cbzo DL.Val.OH	H.L.Phe.OCH₃	THF	71**	460
	H.DL.Phe.OH	Dioxane	—	461
	H.DL.Phe.OCH₃	Dioxane	32	133
	H.Gly.OH	Dioxane	25	133
	H.Gly.OC₂H₅	Ether	60	20
	H.Gly.SC₂H₅	Ether	83	20
	H.DL.Ala.OH	Dioxane	60	37
	H.DL.Ala.OC₂H₅	Dioxane	71	20
	H.DL.Val.OH	Ether	86	20
	H.DL.Val.OC₂H₅	Ether	60	20
	H.DL.Leu.OH	Ether	80	20
	H.DL.Leu.OC₂H₅	Dioxane	75	20
	H.DL.Nva.OH	Ether	75	20
	H.DL.Nva.OC₂H₅	Dioxane	70	20
Cbzo.Val.OH	H.β.DL.L.Cys.OC₂H₄Cl	Chloroform	70	452, 454
Cbzo.DL.Val.OH	H.L.Asp(OC₂H₅)₂	Ether	70	20
	H.L.Glu(OH)₂	Dioxane	58	20
	H.L.Glu(OC₂H₅)₂	Ether	45	20

Toz
↓
H.L.Orn.OH

Cbzo.L.Val OH	H.L.Orn.OH	Dioxane	48	131

Note: References 437 to 524 are on pp. 333–335.

‡ This is the yield after saponification.

† The product is benzyl carbobenzyloxy-D-seryl-L-leucinate. See Fölsch, Acta Chem. Scand., 13, 1422 (1959).

** This is the yield after saponification and hydrogenolysis.

TABLE II—Continued
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.L.Val.OH (continued)	H.L.Orn.OCH$_3$ (Tos)	Dioxane	78	131
Cbzo.DL.Val.OH	H.DL.Phe.OH	Dioxane	62	20
	H.DL.Phe.OC$_2$H$_5$	THF	80	462
	H.DL.Phe.OC$_2$H$_5$	Ether	80	20
Cbzo.L.Val.OH	H.L.Tyr.OCH$_3$	THF	70	460
	H.DL.Try.OCH$_3$	Chloroform	73	446, 447
(C$_6$H$_5$CH$_2$)$_2$.DL.Nval.OH	H.Gly.NH$_2$	THF	67	84, 463
Cbzo.L.Leu.OH	H.L.Val.OH	THF	41	464
	H.S.Bz.L.Cys.OH	THF	47	465
	H.S.Bz.L.Cys.OC$_2$H$_5$	Chloroform	75	466
	H.L.L.Asp.OH (NH$_2$)	Dioxane	55–80	66, 415
	H.im.C$_6$H$_5$CH$_2$.L.His.OCH$_3$	—	—	450
	H.D.Phe.OH	Dioxane	62	131, 153
	H.D.Phe.OCH$_3$	Dioxane	70	131
Phth.L.Leu.OH	H.L.L.Asp.OH (NH$_2$)	Dioxane	65	66
	H.L.Glu.OH (NH$_2$)	Dioxane	30	66

		Solvent	Yield	References
$(C_2H_5CH_2)_2$-DL-Leu-OH	H.DL.Tyr.OCH₃	Chloroform	50	446, 447
	Cbzo | H.L.Lys.OCH₃	Chloroform	62	407
C_2H_5O-C.DL.Ileu.OH	H.DL.Ser.OCH₃	Chloroform	—	18
Cbzo DL.Ileu.OH	H.L.Ileu.OCH₃	THF	58	460
Cbzo L.Ileu.OH	H.ε-CbzL.Lys.NH₂.OCH₃.C₂H₅	THF	10	227
	H.L.Phe.OCH₃	Chloroform	78	18
	H.L.Phe.OCH₃		Low	454
	H.S.Bz.L.Cys.OCH₃	Chloroform	72	348, 451
	H.Gly.OC₂H₅	Chloroform	77	451
	H.Oly.OC₂H₅	Chloroform	80	454–460
	H.L.Ala.OCH₃	THF	51	454
	H.L.Ala.OCH₃	Chloroform	Low	348
HCO.S.Bz.L.Cys.OH	H.S.Bz.L.Cys.OH	Chloroform	39–97	454
Cbzo.S.Bz.L.Cys.OH	H.S.Bz.L.Cys.OCH₃	Chloroform	57	348, 454
	H.S.Bz.L.Cys.OC₂H₅			348
(a) [structure] SCH₂CH₂NH₂.CO.CH₃	H.S.Bz.L.Cys OC₂H₅.C₆H₅	Methylene dichloride	87	432
	H.L.Phe.OCH₃	Chloroform	60	406
	H.L.Tyr.NH₂	Chloroform	20	406
	NH₂ | H.L.Asp.OH	Dioxane	—	68
	H.L.Tyr.OCH₃	THF	50–70	81
	H.L.Tyr.OC₂H₅	THF	13‡	200

Note: References 431 to 538 are on pp. 353–355.

‡ This is the yield after saponification.

TABLE II—*Continued*

ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Bis-(carbobenzyloxy)-L-cystine	H.Gly.OC$_2$H$_5$	THF	57	459
Bis-(p-nitrocarbobenzyloxy)-L-cystine	H.Gly.OC$_2$H$_5$	THF	75	468
	H.L.Phe.OC$_2$H$_5$	THF	81	468
Cbzo.L.Met.OH	H.Gly.OC$_2$H$_5$	Dioxane	77	469
	H.L.Glu(OC$_2$H$_5$)$_2$	Dioxane	82	469, 470
Phth.L.Met.OH	H.L.Glu.OH $\overset{\displaystyle\text{OCH}_2\text{C}_6\text{H}_5}{\vert}$	THF	42††	471
HCO.L.Phe.OH	H.Gly.OC$_2$H$_5$	Methylene dichloride	50	133
	H.Gly.NHC$_6$H$_5$	Methylene dichloride	56	133
Cbzo.DL.Phe.OH	H.Gly.OCH$_3$	Dioxane	80	288, 314
	H.Gly.OC$_2$H$_5$	THF	87	157, 440
	H.DL.Glu(OC$_2$H$_5$)$_2$	Dioxane	80	472
	H.L.Lys.OCu/2	THF	52	61
	H.L.His.OCH$_3$	Chloroform	80	18
Cbzo.L.Phe.OH	H.*im*.C$_6$H$_5$CH$_2$.L.His.OCH$_3$	Chloroform	70	227, 450
	H.*im*.C$_6$H$_5$CH$_2$.L.His.OCH$_2$C$_6$H$_5$	THF	61	227
	H.NO$_2$.L.Arg.OCH$_3$	Dioxane	70	438, 439,
Cbzo.DL.Phe.OH	H.DL.Phe.OH	Dioxane	31	473
	H.DL.Phe.OC$_2$H$_5$	Dioxane	74	472

		Solvent	24	32
Phth.L.Phe OH	(±) H₃C— CHCO₂CH₃ (NH, C, S, H₃C, CH₃)	Methylene dichloride-dioxane		32
Cbzo.O.Cbf.L.Tyr.OH	H.Gly.OC₂H₅	Chloroform-DMF	73	123
Cbzo.L.Try.OH	H.Gly.OH	THF	70	450
	H Gly.OC₂H₅	THF	60	450
OC₂H₅ / C₂H₅CO.DL.Asp OH	H.Gly.NH.C₁₀H₁₄*	Chloroform-dioxane	80	101, 473a
OCH₃ / Cbzo.L.Asp OH	H.Gly.NHC₁₀H₁₄*	Chloroform-dioxane	00	101
	H NO₂.L.Arg.OH	THF	51	460
OCH₃ / Cbzo.L.Asp OH	H.Gly.OCH₂C₆H₅	Dioxane	50	416
OCH₃ / Cbzo.L.Asp OH	H Tos.L.Lys.OCH₂C₆H₅ ††	Chloroform	57	474

Note: References 497 to 538 are on pp. 353-355.

†† This is the yield after removal of the phthaloyl group.

TABLE II—*Continued*

ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.L.Asp.OCH₂C₆H₅ OH	H.Tos.L.Lys.OCH₂C₆H₅ H	Chloroform	—	474
Phth.DL.Asp.OCH₃ OH	p-H₂NC₆H₄CO₂H p-H₂NC₆H₄CO₂C₂H₅	Dioxane Dioxane	66 87	445 445
Cbzo.L.Asp.OH NH₂—OC₂H₅	H.L.Ser.OCH₃	Chloroform	22	110
C₆H₅CO.DL.Glu.OH	H.Gly.NHC₆H₁₃-n	Chloroform-dioxane	84	101
Cbzo.L.Glu.OH OCH₃	H.Gly.OC₂H₅ H.L.Ala.OH H.L.Glu(OC₂H₅)₂ NH₂ H.L.Glu.OH	Chloroform — Chloroform —	72 — 68 37	317 474a 317 475

OCH$_2$C$_6$H$_5$ | Cbzo·L·Glu·OH	H·L·Ala OCH$_2$C$_6$H$_5$	Dioxane	70‖	96
OH	H·L·Glu(OCH$_2$C$_6$H$_5$)$_2$	Dioxane	70‖	96
| Cbzo·L·Glu OCH$_2$C$_6$H$_5$	H·L·Ala OCH$_2$C$_6$H$_5$	Dioxane	70‖	98
OH |	H·L·Glu·OCH$_2$C$_6$H$_5$	Dioxane	35	97
NH$_2$	II L·Glu(OCH$_2$C$_6$H$_5$)$_2$	Dioxane	70‖	96
| Cbzo·L·Glu·OH	II S·D$_2$·L·Cys·OCH$_3$	THF-dioxane	56	83
(Tbzo)$_2$ D$_2$·L·Lys OH	II.9 D$_2$·L·Cys·OC$_2$H$_5$	THF	>35	155
	II.DL·Val·OC$_2$H$_5$	THF	62	402
(Tbzo)$_2$ L·Lys OH	II.D$_2$·Val·OCH$_2$C$_6$H$_5$	THF	60	402
	II.L·Lys·OC$_2$H$_5$	THF	50	01
Cbzo |	II.NO$_2$·L·Arg·OCH$_3$	Dioxane	64	438, 439
Tos·L·Lys·OH	F·H·NO$_2$L·CO$_2$CH$_2$C$_6$H$_5$	THF	21	100
	II·Gly·OC$_2$H$_5$	Dioxane	14	11
(Tbzo)$_2$ L·Arg·OH	II·L·Glu(OCH$_2$C$_6$H$_5$)$_2$	Chloroform	11	11
		Chloroform	75	93
				83, 94

Note: References 437 to 438 are on pp. 353–355.
Other optical isomers were prepared.

		Yield	Solvent	Ref.
n-C₄H₉CH(OH)NHC₆H₅CH₂CO₂H	n-i-C₆H₅NCH(CH₃)₂CH₂CO₂H	74	THF	453
i-C₃H₇CH(OH)NHC₆H₅CH₂CO₂H	n-i-C₆H₅CH₂CH₃NH₂CH₂CO₂H	90	THF	453
C₆H₅·NH(CH₃)CH(NH)C₆H₅CO₂CH₂CO₂H	n-i-C₆H₅CH₂C₆H₅CH₂CO₂H	56§	THF	457
Dicarbobenzoxy-3,5′-(p-phenylene)di-alanine	H₂·Ala.OCₙH₅	92	THF	453
	H₂·Gly.OCₙH₅	70	THF	470
	H₂·Gly.OCₙH₅			
(±) H₂C⁻⁻⁻CH(CO₂H)	H₂·Gly.OCH₃	30	Chloroform	31
N XₓHₓO	H₂·Gly.OCH₃	80	Methylene di-chloride-dioxane	32
CₙH₅O CH₃				
C₆H₅n.Ala.OH	H₂.n.Ala.Gly.SCₙH₅	63	THF	37
	H·LPro.Gly.OCₙH₅	80 crude	Chloroform	59
C₆H₅n.Ala.OH	H₂.LPro.Gly.OCₙH₅	80 crude	Chloroform	59
	H₂·Gly.Gly.OH	59	THF	337
	OH			
	H L·Glu.L.Ala.OH			
C₆H₅·L·Pro·OH	H Gly.Gly.OCₙH₅	07	Dioxane	07
	H·L.Leu.Gly.SNH₂	55∥	Chloroform	50
C₆H₅n.Val.OH	H₂·Gly.Gly.OH	87 crude	THF	81, 403
	OH	61	Dioxane	20
	H L.Glu.L·Val.OH			
C₆H₅·L·Val·OH	H₂·L·Glu L·Val·OH	60		
		58	Toluene	480

Note: References 457 to 534 are on pp. 351–355.

§ This is the yield after hydrogenolysis

∥ Other optical isomers were prepared.

TABLE II—Continued
ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.L.Leu.OH	H.S.Bz.L.Cys.Gly.OCH₂C₆H₅	Chloroform	50	154
	H.S.Bz.L.Cys.L.Tyr.NH₂	Chloroform	90	166
	(OH) H.L.Glu.L.Leu.OH	Toluene	43	150
Cbzo.S.Bz.L.Cys.OH	H.Gly.Gly.OCH₃	Chloroform	27	336
	H.Gly.Gly.OC₂H₅	Chloroform	56	336
	H.L.Ala.L.Ser.OCH₃	Chloroform	—	151,456
Cbzo.Phe.OH	H.Gly.Val.OCH₃	Chloroform	87	181
Cbzo.DL.Phe.OH	H.DL.Glu.DL.Phe.OH	Dioxane	51	172
(NH₂) Cbzo.L.Asp.OH	H.L.Ser.Gly.OC₂H₅	Chloroform	9	110
	(H) C₂H₅O₂C.DL.Heu.L.Lys.OCH₃ Tos.DL.Ileu	Chloroform	93	167
	H.L.Lys.OCH₃	Chloroform	17	167
(OCH₃) Cbzo.L.Glu.OH	H.Gly.L.Glu(OC₂H₅)₂	Chloroform	75	317

$\overset{OC_2H_5}{\underset{\mid}{Cbzo\cdot L\cdot Glu\cdot OH}}$	$\overset{OCH_3}{\underset{\mid}{H\cdot L\cdot Glu\cdot Gly\cdot OC_2H_5}}$	Chloroform	70	317
$\overset{OC_2H_5}{\underset{\mid}{Cbzo\cdot L\cdot Glu\cdot OH}}$	$\overset{NH_2,\ NH_2}{\underset{\mid}{H\cdot L\cdot Glu\cdot L\cdot Glu\cdot OH}}$	Chloroform	53	475
	$\overset{}{\underset{}{H\cdot L\cdot Gly\cdot L\cdot Glu\cdot OC_6H_5)_2}}$			
$\overset{NH_2}{\underset{\mid}{Cbzo\cdot L\cdot Glu\cdot OH}}$	$\overset{OH}{\underset{\mid}{H\cdot L\cdot DL\cdot Glu\cdot DL\cdot Phe\cdot OH}}$	Chloroform	54	317
	$\overset{NH_2}{\underset{\mid}{H\cdot L\cdot Asp\cdot S\cdot Bz\cdot L\cdot Cys\cdot OH}}$	Dioxane	40	472
$\overset{NH_2}{\underset{\mid}{Cbzo\cdot L\cdot Glu\cdot OH}}$	$\overset{NH_2}{\underset{\mid}{H\cdot L\cdot Asp\cdot S\cdot Bz\cdot L\cdot Cys\cdot OCH_3}}$	THF-dioxane	61	84
	$\overset{NH_2}{\underset{\mid}{H\cdot L\cdot Cys\cdot S\cdot Bz\cdot L\cdot Cys\cdot OCH_3}}$	THF-dioxane	72	84, 467
(Cbzo)₂·DL·Lys·OH	H·DL·Val·DL·Phe·OC₆H₅	THF-dioxane	63	83
p·NO₂·Cbzo·NG₂,L·Arg·OH	H·L·The·L·Ser·OC₂H₄	THF	17	402
CCH₂O·Gly·Gly·OH	H·Gly·OH	THF	65	92
Cbzo·ASCH₂C₆H₅	H·Obj·OCH₂C₆H₅	Dioxane	10	482
Cbzo·Gly·Gly·OH		—	50	314
	H·L·Glu·OH	Chloroform	24	101

Note: References 437 to 538 are on pp. 353–356.

TABLE II—*Continued*

ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Tri.Gly.Gly.OH	H.DL.Phe.OC₂H₅	Benzene	14	9, 10
Cbzo.DL.Ala.Gly.OH	H.Gly.SC₂H₅	THF	48	37
Cbzo.Phe.Gly.OH	H.Leu.OCH₃	Chloroform	26	314
Cbzo.Gly.Ala.OH	H.S.Bz.L.Cys.OH	THF	22	299
Cbzo.Gly.DL.Val.OH	H.Gly.OH	THF	57	125
	H.DL.Ala.SC₂H₅	THF	76	45
	H.DL.Leu.SC₂H₅	THF	63	45
	H.DL.Ileu.SC₂H₅	THF	41	45
Cbzo.DL.Val.DL.Val.OH	H.Gly.OC₂H₅	Ether	72	5
	H.DL.Val.OC₂H₅	Ether	24	5
Cbzo.L.Leu.L.Val.OH	H.L.Glu(OC₂H₅)₂	THF	41	361
Cbzo.Gly.Leu.OH	H.Gly.OCH₃	Chloroform	72	362
	H.Phe.OCH₃	Chloroform	77	314
Cbzo.DL.Val.DL.Leu.OH	H.Gly.OC₂H₅	Ether	35	5
Cbzo.DL.Val.DL.Nleu.OH	H.Gly.OC₂H₅	Ether	41	5
Cbzo.Gly.Phe.OH	H.Leu.OCH₃	Chloroform	44	314
Cbzo.Gly.DL.Phe.OH	H.DL.Ser.OCH₃	THF	71	181
Cbzo.DL.Val.DL.Phe.OH	H.Gly.OC₂H₅	Ether	73	5
Cbzo.L.Leu.D.Phe.OH	H.DL.Leu.OC₂H₅	Ether	36	5
Cbzo.DL.Phe.DL.Phe.OH	H.L.Pro.OCH₃	Chloroform	72	153
	H.DL.Glu(OC₂H₅)₂	Dioxane	73	122
	H.L.Glu(OCH₂C₆H₅)₂	Dioxane	63	122
Cbzo.S.Bz.L.Cys.L.Tyr.OH	H.L.Val.OCH₃	THF	77	91, 163
	H.L.Leu.OCH₃	THF	68	91
	H.L.Ileu.OCH₃	THF	68	91
	H.L.Phe.OCH₃	THF	68	91
(C₆H₅CH₂)₂.DL.Ala.DL.Try.OH	DL.C₆H₅CH₂CH(NH₂)CO₂C₂H₅	Chloroform	88	110, 145

	OH				
Cbz.L.Ala L.Glu.OCH₂C₆H₅	H.L.Ala.OCH₂C₆H₅	Dioxane	70‖	97	
	OH				
Cbz L.Glu L.Ala.OCH₂C₆H₅	H.Gly.OCH₃C₆H₅	Dioxane	70‖	97	
Tn Gly.imₓC₂H₄Cl₂.L.Ilₐ.OH	H.L.Ala.OCH₂C₆H₅	Dioxane	70‖	97	
Cbz.L.Phe.NO₂.L.Arg.OH	H.L.Leu.OCH₂C₆H₅		—	450	
Cbz.Gly OH	H.L.Try.OCH₂C₆H₅		1	430, 473	
Cbz.S.Bz.L.Cys OH	H.L.Leu S Bz L.Cys.L.Tyr NH₂	Chloroform	70	400	
	OCH₂C₆H₅	H.Gly.Gly.Gly OC₂H₅	Chloroform	75	348
Cbz.L.Glu.OH	H.L.Bzₓ.Phe.NO₂.L.Arg.OH	Dioxane	57	465	
Cbz.Gly.Gly.OH	H.Gly.L.Pro OC₂H₅	Chloroform	14§	59	
Cbz.L.Ala.OC₃H₇OH	H.Val S.Bz.L.Cys.OCH₂C₆H₅	Chloroform	64	452	
Phth.Gly.L.Phe.OH	H.Gly.L.Leu.OH	Dioxane	67	54	
Cbz L.Ala L.Phe.OH	H.L.Pro.L.Leu.OCH₃		70	60	
Cbz.Gly.Gly Gly OH	H.L.Pro.OC₂H₅	Chloroform	10§	60	
Cbz.Gly.Gly.L.Glu OH	H.Gly.NH₂C₁₀H₇ᵃ	Dioxane-toluene	70	101	
Phth.Gly.Gly.Gly.OH	H.Gly OC₂H₅	Water-nitrobenzene	50	125	

Note: References 437 to 528 are on pp. 353–355.

§ This is the yield after hydrogenolysis.

‖ Other optical isomers were prepared.

TABLE II—*Continued*

ANHYDRIDE FORMATION WITH ETHYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Ref.
Cbzo.Gly.L.Leu.OH	H.Gly.Leu.Gly.OCH$_3$	Chloroform	66	242
Cbzo.L.Leu.S.Bz.L.Cys.OH	H.L.Leu.L.Val.L.Glu(OCH$_2$C$_6$H$_5$)$_2$	Methylene dichloride	20	465
Cbzo.Gly.DL.Val.Gly.OH	H.Gly.DL.Val.Gly.OH	THF	44	483
Cbzo.Gly.DL.Val.DL.Ala.OH	H.Gly.DL.Val.DL.Ala.SC$_6$H$_5$	THF	76	37
Cbzo.Gly.Gly.DL.Phe.OH	H.Gly.Gly.DL.Phe.OC$_2$H$_5$	DMF	66	149

Cbzo.L.Ala.L.Phe.L.Pro.L.Leu.OH
  |
OC$_2$H$_5$
	H.L.Glu.L.Phe.OCH$_3$
	  |
	OC$_2$H$_5$
		—	39	60

Cbzo.L.Glu.OH | OCH$_3$	H.L.Ala.L.Phe.L.Pro.L.Leu.L.Glu.L.Phe.OCH$_3$	—	36	60
Cbzo.L.Asp.NO$_2$.L.Arg.OH	H.L.Val.L.Tyr.L.Ileu.L.His.L.Pro.L.Phe.OCH$_3$	Dioxane	36	460
Cbzo.[NH(CH$_2$)$_5$CO]$_2$.OH	H[NH(CH$_2$)$_5$CO]$_6$.OCH$_3$	—	—	486
Cbzo.S.Bz.L.Cys.Gly.Gly.DL.Lys.OH | Cbzo	CO$_2$.cyclohexyl H.Gly.Gly.DL.Lys.S.Bz.L.Cys.OCH$_3$	—	—	487
Cbzo[NH(CH$_2$)$_5$CO]$_3$.OH	H[NH(CH$_2$)$_5$CO]$_6$.OCH$_3$	—	—	486

Note: References 437 to 538 are on pp. 353–355.

TABLE III

ANHYDRIDE FORMATION WITH sec-BUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.DL.Val.OH	Toluene	49	21, 50
	H.DL.Phe.OH	Toluene	63	50
	H.DL.Phe.OC$_2$H$_5$	Chloroform-toluene	71	21, 150, 151
Phth Gly.OH	H.L.Tyr.OC$_2$H$_5$	Toluene	51	21
	H.L.Leu.OC$_2$H$_5$	Toluene	57	21, 50
CH$_3$CO.DL.Ala OH	H.L.Tyr.OC$_2$H$_5$	Toluene	58	21
Cbzo.L. Ala.OH	H.DL.Phe.OH	THF*	50	483
	H.DL.Phe.OC$_2$H$_5$	Toluene	50	21, 58
Cbzo L.Pro.OH	H.L.Pro.OH	Toluene	41	21
Cbzo.DL.Val.OH	H.DL.Ala OC$_2$H$_5$	Chloroform	86	109
	H.DL.Ala OC$_2$H$_5$	Toluene	05	21
	H L.Leu OC$_2$H$_5$	Toluene	08	21
	H.DL.Phe.OC$_2$H$_5$	Toluene	47	21
	Cbzo			
Phth.L.Val.OH	H.L.Orn.OCH$_3$	THF	83 crude	07
Cbzo L Leu OH	L.Gly OC$_2$H$_5$	Chloroform	86	21, 150, 151, 169
	H.L.Leu.OCH$_3$	Toluene	64	21, 150, 151
Phth.DL.Leu.OH	H L.Tyr OC$_2$H$_5$	Toluene	63	21, 56, 108
Cbzo.L.Phe.OH	H DL.Phe.OC$_2$H$_5$	Toluene	55	21
(Cbzo)$_2$L Lys OH	H L.Tyr OC$_2$H$_5$	Toluene	46	21, 150, 151
	H Gly.OC$_2$H$_5$	Toluene	64	21, 150, 151

Note: References 437 to 538 are on pp. 353-355.

* THF is tetrahydrofuran.

TABLE III—*Continued*

Anhydride Formation with *sec*-Butyl Chloroformate

Acid	Amine	Solvent	Yield, %	References
Cbzo | Tos.L.Lys.OH	p-H₂NC₆H₄CO₂CH₂C₆H₅	THF	0	100
dl-CbzoNHCH₂CH(NHCbzo)CO₂H	H.Gly.OC₂H₅	Chloroform	74	489
Cbzo.dl.S.Bz.homo.Cys.OH	H.Gly.OC₂H₅	Toluene	59†	490
Cbzo.L.Pro.OH	H.L.Leu.Gly.OC₂H₅	Chloroform	79	169
Phth.dl.Phe.OH	H.Gly.Gly.OC₂H₅	Toluene	97	21, 56, 150, 151, 198
Cbzo.Gly.dl.Phe.OH	H.Gly.OC₂H₅	Chloroform-toluene	70	21
(L) O=⟨ring⟩ N(Tos)CO.L.Glu.OH (NH₂)	H.L.Ala.OCH₂C₆H₅	DMF‡	85	401
Cbzo.S.Bz.L.Cys.OH	H.L.Pro.L.Leu.Gly.NH₂	Chloroform	80	169
Cbzo.Gly.dl.Phe.Oh	H.Gly.dl.Phe.OH	Chloroform-toluene	95	21, 150, 151
Cbzo.dl.Ala.dl.Phe.OH	H.dl.Val.L.Leu.OC₂H₅	Chloroform-toluene	30	21
Cbzo.Gly.dl.Phe.OH	H.dl.Phe.Gly.Gly.OC₂H₅	Chloroform-toluene	50	21, 56, 150
Cbzo | Phth.L.Val.L.Orn.OH	H.L.Leu.D.Phe.L.Pro.OOH₃	THF	63	153

Note: References 437 to 538 are on pp. 353-355.

† Other optical isomers were prepared.

‡ DMF is dimethylformamide.

TABLE IV

ANHYDRIDE FORMATION WITH ISOBUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
$(CH_3)_2CHOCO.Gly.OH$	H.DL.Phe.OCH$_3$	Acetone	95	05
$(CH_3)_2COCO.Gly.OH$	H.DL.Phe.OCH$_3$	Acetone	78	28
$(CH_3)_2CHOCO.Gly.OH$	H.Gly.OCH$_3$	Acetone	82	28
Cbzo.DL.Phe.OH	H.DL.Phe.OCH$_3$	Acetone	61	28
	H.Gly.OCH$_3$	Acetone	71	65
	H.DL.Phe.OH	Toluene	63	21
	H.DL.Phe.OCH$_3$	Acetone	81	05
	H.DL.Phe.OCH$_3$	Toluene	64	21
	H.L.Tyr.OC$_2$H$_5$	Toluene	68	21, 56, 150, 151
Cbzo H.L.Lys.OCH$_2$C$_6$H$_5$		Ethyl acetate	70	132
Phth.Gly.OH	H.SO$_4$.L.Arg.OH	Toluene	40	492
	H.Gly.OH	Chloroform	72	152
	H.Gly.OC$_2$H$_5$	Chloroform	85	152
	H.DL.Ala.OH	Chloroform	82	152
	H.L.Leu.OC$_2$H$_5$	Toluene	57	21
	H.L.Tyr.OC$_2$H$_5$	Toluene	58	21
$(CH_3)_2COCO.DL.Ala.OH$	H.Gly.OC$_2$H$_5$	Acetone	50	28
Cbzo.DL.Ala.OH	H.Gly.OCH$_3$	Acetone	08	28
Cbzo D.Ala.OH	H.Gly.OCH$_3$	Acetone	08	05
	H.DL.Ala.OC$_2$H$_5$	Chloroform-toluene	Low	67

Note: References 437 to 538 are on pp. 353-355.

TABLE IV—Continued

Anhydride Formation with Isobutyl Chloroformate

Acid	Amino	Solvent	Yield, %	Refs.
Cbzo.β.Ala.OH	H.DL.Phe.OCH₃	Acetone	90	65
	H.Glu(OH)₂	DMF*	55	122
	DL-3-(2-Thienyl)alanine	Acetone	75	493
Cbzo.L.Pro.OH	Tos | H.L.Lys.OH	THF†	47	494
Cbzo.allo.HO.L.Pro.OH	H.Gly.OC₂H₅	Ethyl acetate	—	495
(CH₂)₃COCO.DL.Val.OH	H.Gly.OCH₃	Acetone	72	28
(CH₂)₄CHOCO.L.Val.OH	H.Gly.OCH₅	Acetone	68	28
	H.Gly.OCH(CH₂)₄	Acetone	77	28
	H.L.Ser.OCH₃	Acetone	44	28
Cbzo.DL.Val.OH	H.Gly.OCH₃	Acetone	92	65
(CH₂)₄CHOCO.DL.Nval.OH	H.Gly.OCH₃	Acetone	66	28
	H.Gly.OCH(CH₂)₄	Acetone	63	28
(CH₂)₃COCO.L.Leu.OH	H.Gly.OCH₃	Acetone	80	28
	H.L.Leu.OO₂H₅	Acetone	48	28
(CH₂)₃CHOCO.L.Leu.OH	H.Gly.OCH(CH₂)₄	Acetone	70	28
	H.L.Leu.OC₂H₅	Acetone	64	28
Cbzo.L.Leu.OH	H.Gly.OC₂H₅	Toluene	53	21
	H.L.Ala.OH	THF	62	124
	H.L.Leu.OOH₃	Toluene	71	21
	H.L.Tyr.OC₂H₅	THF	83	496
	H.L.Tyr.OCH₂O₅H₅	THF	80	496
(CH₂)₄CHOCO.L.Ileu.OH	H.Gly.OCH₃	Acetone	52	28
(CH₂)₃CHOCO.DL.Ileu.OH	H.DL.Val.OCH₃	Acetone	61	28
	H.DL.Ser.OCH₃	Acetone	63	28

(CH₃)₂CHCO.L-Ileu OH	H.Ileu.OCH₃	Acetone	44	28
(CH₃)₂CHCO.D-L-Nleu OH	H.Gly.OCH(CH₃)₂	Acetone	69	28
Cbzo S.Bz.L-Cys OH	H₂.Cys.OH	THF	45	452
H.S Br L-Cys.OH	H.S Br L.Cys.OC₂H₅	Chloroform-toluene	67‡	170
Phth.S.Bz.Cys.OH (DL + L)	H.Gly.OH	—	70	497
(CH₃)₂CHCO.D-L.Met.OH	H.Gly.OCH₃	Acetone	71	28
Cbzo.Met.OH	H.Gly.OC₂H₅	Acetone	78	65
(CH₃)₂CHCO.D-L.Phe.OH	H.β.Ala.OC₂H₅	Acetone	35	28
	H.Gly.OCH₃	Acetone	71	28
	H.Gly.OCH₃	Acetone	72	28
	H.Gly.OC₂H₅	Toluene	48	57
	H.Gly.OC₂H₅	Toluene	50	40
	H.Gly.OCH₂C₆H₅	Toluene	57	402
	H.NO₂.L-Arg.OH	Acetone	53	28
	H Gly.NH₂	Dioxane	55	498
	Cbzo			
	H.L.Lys.OH	THF	37	124
(CH₃)₂CHCO.L.Asp.OH NH₂	H.L.6m(OC₂H)CH₃)₂Ala)	Acetone	20	28
OH				
Cbzo.L.Asp.NH₂	H.S.Bz.L.Cys.OCH₂C₆H₄.	THF	82	499

Note: References 437 to 638 are on pp. 353–355.

* DMF is dimethylformamide.
† THF is tetrahydrofuran.
‡ Other optical isomers were prepared.

TABLE IV—*Continued*

ANHYDRIDE FORMATION WITH ISOBUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
	NH_2			
	|			
Cbzo.L.Glu.NH_2	H.L.Asp.OH	THF	41	500
(Cbzo)$_2$.L.Lys.OH	H.Gly.OCH$_3$	Ethyl acetate	32	132
	H.Gly.OC$_2$H$_5$	Toluene	64	21
	H.L.Val.OH	THF	65	57
	H.L.Val.OC$_2$H$_5$	Toluene	81	57
	Cbzo			
	|			
	H.L.Lys.OCH$_2$C$_6$H$_5$	Ethyl acetate	89	132
Cbzo.NO$_2$.L.Arg.OH	H.Gly.OC$_2$H$_5$	THF	28	492, 501
	H.Gly.OCH$_2$C$_6$H$_5$	THF	58	492, 501
	H.L.Leu.OCH$_3$	THF	53	492, 501
	H.L.Phe.OC$_2$H$_5$	THF	41	492, 501
	H.L.Tyr.OC$_2$H$_5$	THF	60	492
	H.L.Glu(OC$_2$H$_5$)$_2$	THF	82	492, 501
	H.Gly.OH	Chloroform	0	31
	H.Gly.OCH$_3$	Chloroform	67	31
	H.Gly.NH_2	Dioxane	90	497
(L) H$_2$C——CHCO$_2$H				
| |				
S NCHO				
\ /	H.Gly.OCH$_3$	Toluene	47	490
C	H.D.Val.OH	THF	31	490
/ \	H.L.Glu(OC$_2$H$_5$)$_2$	Dioxane	33	490
H$_3$C CH$_3$	H.Gly.OCH(CH$_3$)$_4$	Acetone	76	28
Cbzo.DL.S.Bz.homo.Cys.OH				
(CH$_3$)$_3$CHOCONH(CH$_2$)$_5$CO$_2$H				

Acyl component	Amino component	Solvent	Yield	Reference
CbzNH(CH₂)₄CO₂H	H₂N(CH₂)₄CO₂H	THF	83	273
(CH₃)₂CHOCONH(C₆H₄)CO₂H	H.Gly.OCH(CH₃)₂	Acetone	84	28
(CH₃)₂CHOCO.Gly.OH	H.L.Leu.Gly.OCH(CH₃)₂	Acetone	63	28
(CH₃)₂CHOCO.Gly.OH	H.L.Leu.Gly.OCH₃	Acetone	98	28
(CH₃)₂CHOCO.L.Val.OH	H.L.Leu.Gly.OC₂H₅	Acetone	65	28
Cbz.L.Val.OH	H.L.Phe.Gly.OC₂H₅	Toluene		57
CbzO.L.Asp.OCH₂.C₆H₅ (OH) (OC₂H₅)	H.S.Bz DL homo Cys.Gly.OC₂H₅	Toluene	71	502
Cbz.L.Glu.OH (OH)	H.S.Bz DL homo Cys Gly OC₂H₅	Dioxane	34	502
	H.S.Bz DL homo Cys Gly OC₂H₅	Toluene	67	502
Pbth.L.Glu.OCH₃	(±) H₂O·····CH.CON.CH.CO.OCH₃ (ring: NH, C, CH₃, S, H₂O, NH₂)	Chloroform	—	497
(NH₂)	H.L.Asp.β.Et.L.Cys.OCH₃	THF	81	87
CbzO.L.Glu.OH	H(NH(CH₂)₃SO₃H	THF	87	273
	H.Gly.OCH₃	Toluene	69	40
CbzO.Gly.L.Leu.OH	H.Gly.OH	THF	39	57
Cbz.Gly.L.Phe.OH	H.Gly.OCH₃	Toluene-dioxane	77	40

Note: References 437 to 538 are on pp. 353–355.

TABLE IV—*Continued*

ANHYDRIDE FORMATION WITH ISOBUTYL CHLOROFORMATE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.Gly.DL.Phe.OH	H.Gly.OC₂H₅	Chloroform-toluene	83	21, 56, 150, 151
Cbzo[NH(CH₂)₅CO]₂OH	H₂N(CH₂)₅CO₂H	THF	76	273
O,N-(Cbzo)₂.L.Tyr.OH	H.L.Phe.L.Glu.L.Asp.OH (NH₂ NH₂)	THF	71	82
N-Cbzo-O-Tos.L.Tyr.OH	H.L.Phe.L.Glu.L.Asp.OH (NH₂ NH₂)	THF	79	81
(Cbzo)₂.L.Lys.OH	H.L.Val.L.Phe.Gly.OC₂H₅	Toluene	70	57
Cbzo.Gly.Gly.OH	H.Gly.L.Lys.OCH₃ (Cbzo)	THF	67	503
(Cbzo)₂.L.Lys.L.Val.OH	H.L.Phe.Gly.OH	THF	29	57
	H.L.Phe.Gly.OC₂H₅	THF	54	57
Cbzo[NH(CH₂)₅CO]₂OH	H[NH(CH₂)₅CO]₂OH	—	—	273
Cbzo[NH(CH₂)₅CO]₂SC₆H₅	H[NH(CH₂)₅CO]₂SC₆H₅	DMF	64	273
	H₂N(CH₂)₅CO₂H	DMF	83 crude	273
Cbzo.S.Bz.L.Cys.OH	H.L.Tyr.L.Phe.L.Glu.L.Asp.OH (NH₂ NH₂)	THF	87 crude	82
	H.O-Tos.L.Tyr.L.Phe.L.Glu.L.Asp.OH (NH₂ NH₂)	THF	83	81

Cbzo.Leu.L.Ala.OH	H.L.Val.L.Phe.Gly.OC$_2$H$_5$ (NH$_2$, NH$_2$)	THF	70	124
Cbzo.S.Bz.L.Cys.L.Phe OH		—	—	504
Cbzo.S.Bz.L.Cys.L.Tyr.OH	H.L.Ileu.L.Glu.L.Asp.OH (NH$_2$, NH$_2$)	THF	61 crude	82, 86
	H.L.Phe.L.Glu.L.Asp.OH (NH$_2$, NH$_2$)	THF	62	85, 505
Tos S.Bz.L.Cys.L.Tyr.OH	H.L.Phe L.Glu.L.Tyr.OH	DMF	68	273
Cbzo[NH(CH$_2$)$_4$CO]$_3$OH (Tos)	H[NH(CH$_2$)$_4$CO]$_2$OH / H[NH(CH$_2$)$_4$CO]$_2$SO$_4$H	DMF	—	273
Cbzo.L.Pro.OH	H.L.Val.L.Orn.L.Leu D.Tyr.L.Pro.OCH$_3$ (NH$_2$, NH$_2$)	THF	72	408
N.Tos.S.Bz.L.Cys.L.Tyr.L.Phe.OH	H.L.Glu.L.Asp.S Bz.L.Cys OH	THF-DMF	59	87
Cbzo[NH(CH$_2$)$_4$CO]$_2$OH	H[NH(CH$_2$)$_4$CO]$_2$OH	DMF	64	273
	H[NH(CH$_2$)$_4$CO]$_2$SO$_4$H	DMF	59	273
Cbzo.L.Leu.L.Ala.L.Val.L.Phe.Gly.OH	H L.Pro OCH$_2$C$_6$H$_5$	DMF	60	124
Cbzo.L.Tyr.L.Lys.OH	H.L.Leu.L.Ala.L.Val.L.Phe.Gly.L.Pro.OCH$_2$C$_6$H$_5$	THF	31	124

Note: References 437 to 538 are on pp. 353–355.

TABLE V

ANHYDRIDE FORMATION WITH MISCELLANEOUS CHLOROFORMATES, $ClCO_2R$

R	Acid	Amine	Solvent	Yield, %	Refs.
CH_3	Cbzo.Gly.OH	H.Gly.OH	THF*	Poor	48
$C_3H_7\text{-}i$	Cbzo.L.Glu.OH $\overset{OC_2H_5}{\underset{NH_2}{\mid}}$	H.L.Glu.OH	Acetone	42	491
	Cbzo.L.Glu.OH $\underset{NH_2}{\mid}$	H.L.Ala.OOH$_3$C$_6$H$_5$ $\underset{NH_2}{\mid}$	Acetone	82	491
	Cbzo.L.Glu.OH	H.L.Glu.L.Ala.OH $\underset{OC_2H_5}{\mid}$	Acetone	89	491
	Cbzo.L.Glu.L.Glu.OH $\overset{OC_2H_5\ \ OC_2H_5}{\mid}$	H.L.Glu.OH	THF	51	491
$C_4H_9\text{-}n$	(L) H_3C—S—...—CHCO$_2$H (complex)	H.Gly.OH	Chloroform	0	31

				68	31
(±) H₂C——CHCO₂H			Chloroform		
S NCHO					
C					
‖					
H₂C CH₃		H.Gly.OCH₃			

CH₂C₆H₅	Cbzo.Gly.OH	L-C₆H₅NHCH₂CH₂CHₓNH₂ACO₂C₄H₉			154
	Cbzo-L-Leu.OH	11-L-Leu-OC₆H₅	Chloroform	80	154
	Cbzo-L-NHCH₂CH₂CHNH₂₃CO₂C₆H₅	Cbzo-L-NHCH₂CH₂CHₓNH₂₃CO₂C₄H₉	Chloroform	63	154
	Cbzo-L-NHCH₂CH₂CHNH₂₃CO₂C₆H₅	11-L-OₓₙOC₆H₉	Chloroform	40	154
	Cbzo-L-NHCH₂CH₂CHNH₂₃CO₂C₆H₅	Cbzo.NHCH₂CH₂CHNH₂₃CO₂C₄H₉	Chloroform	70	154
	Cbzo.Gly.Gly.OH	11.Ala.OH	Chloroform	56	154
	(C₆H₅)₃CHCH₂CH₂CH₂CH₂(NHCOCH₃)₃CO₂C₄H₉	H.Ala.OH	Acetone	57	111
C₂H₁₇	Cbzo.Gly-Gly.OH	H.Gly.OH	THF	39	14, 506
	Cbzo.Gly.Ala.OH	H.Gly.OH	THF	68	177, 107, 507, 508
					111
	Cbzo.Gly.Gly.OH	H.Gly.Gly.OH	Acetone– dioxane	18	111
	Cbzo.DL.Ala.Gly.OH	11.DL.Ala.Gly.Gly.OH	THF	40	337
	Cbzo.Gly.Ala.OH	11.Gly.Gly.Ala.OH	Acetone– dioxane	25	111, 509
	Cbzo Gly Gly.Ala.Gly.OH	11.Ala.Gly.OH	DEF†	39	212
	Cbzo-Gly.Ala.Gly.Gly.OH	H.Ala.Gly.Gly.OH	DEF	21	111

Note: References 437 to 538 are on pp. 353–355.

* THF is tetrahydrofuran.

† DEF is diethyl formamide.

TABLE VI

ANHYDRIDE FORMATION WITH ISOVALERYL CHLORIDE

Acid	Amino	Solvent	Yield, %	References
Cbzo.Gly.OH	H.Gly.OH	Dioxane	52	189
	H.DL.Phe.OH	Toluene	—	198, 510
	H.DL.Phe.OC₂H₅	Toluene	86	8, 198, 510
	H.L.Tyr.OC₂H₅	Toluene	77	8, 198, 510
C₆H₅SCO.Gly.OH	H.Gly.OC₂H₅	Toluene	36	444
Phth.Gly.OH	H.L.Leu.OC₂H₅	Chloroform-toluene	62	8
	H.DL.Phe.OC₂H₅	Chloroform-toluene	68	8, 198, 510
	H.L.Tyr.OC₂H₅	Chloroform-toluene	60	8, 198
Cbzo.D.Ala.OH	H.L.Ala.OC₂H₅	Chloroform-toluene	87	67
Cbzo.L.Ala.OH	L-H₂NCH(C₂H₅)CO₂C₂H₅	Chloroform-toluene	>65	67
Cbzo.D.Ala.OH	L-H₂NCH(C₂H₅)CO₂C₂H₅	Chloroform-toluene	>65	67
Cbzo.L.Ala.OH	H.L.Nvnl.OC₂H₅	Chloroform-toluene	>65	67
Cbzo.D.Ala.OH	H.L.Nvnl.OC₂H₅	Chloroform-toluene	>65	67
Cbzo.L.Ala.OH	H.L.Phe.OC₂H₅	Chloroform-toluene	—	67
Cbzo.D.Ala.OH	H.L.Phe.OC₂H₅	Chloroform-toluene	—	67
Cbzo.DL.Ala.OH	H.DL.Phe.OC₂H₅	Chloroform-toluene	48	8, 198, 510
Cbzo.Ala.OH	H.allo.Thr.OH	Dioxane	20	189
n-C₄H₉SCO.DL.Ala.OH	H.Gly.OH	THF*	33	444
Phth.DL.Ala.OH	H.Gly.OC₂H₅	Toluene	74 crude	444
Cbzo.L.Pro.OH	H.DL.Val.OC₂H₅	Chloroform-toluene	40	8
Cbzo.L.Leu.OH	H.L.Leu.Gly.OC₂H₅	Chloroform-toluene	92	199
	H.Gly.OC₂H₅	Chloroform-toluene	70	8, 198, 199, 510
	H.L.Leu.OCH₃	Chloroform-toluene	29	8, 198, 510
	H.DL.Phe.OC₂H₅	Chloroform-toluene	38	8
Cbzo.Nleu.OH	H.L.Tyr.OC₂H₅	Chloroform-toluene	52	8, 198
	H.allo.Thr.OH	Dioxane	20	189

Acid	Amine		Solvent	Yield, %	References
Cbzo.Phe.OH	H.allo.Thr.OH		Dioxane	30	180
n-C4H9SO2.DL.Phe.OH	H.Gly.OC2H5		Toluene	70	444
$\begin{array}{c} NH_2 \\ \| \\ \text{Cbzo.L.Asp.OH} \end{array}$	H.S.Bzl.L.Cys.OCH3	H Gly.OC2H5	THF	5%	87, 223
		H.L.Leu Gly.OC2H5	Chloroform-toluene	5%	M, 108, 510
		H.L.Leu OC2H5	—	92	511
		H.Gly.OC2H5	THF	100 crude	511
			Chloroform-toluene	80	M, 108, 510

Note: References 437 to 538 are on pp. 353-355.

* THF is tetrahydrofuran.

TABLE VII

ANHYDRIDE FORMATION WITH TRIMETHYLACETYL AND DIETHYLACETYL CHLORIDES

Acid Chloride	Acid	Amine	Solvent	Yield, %	References
(CH3)3CCOCl	Cbzo Gly OH	H.DL.Phe.OC2H5	Toluene	81	8, 104
(C2H5)2CHCOCl	Cbzo Gly OH	H.DL.Phe.OC2H5	Toluene	81	8, 108

Note: References 437 to 538 are on pp. 353-355.

TABLE VIII

ANHYDRIDE FORMATION WITH BENZOYL CHLORIDE

Acid	Amino	Solvent	Yield, %	References
Cbzo.Gly.OH	H.DL.Ala.OH	Benzonitrile	71	177, 197, 507, 508, 538
	p-H₂NC₆H₄CO₂H	Benzonitrile	69	178, 512
Phth.Gly.OH	H.Gly.OCH₃	Ether	—	177, 197, 507, 508, 538
	H.Ala.OH	Benzonitrile	83*	172
Cbzo.DL.Ala.OH	H.DL.Phe.OH	Benzonitrile	67*	177, 197, 507, 508, 538
Dicarbobenzyloxy-L-cystine	H.S.Bzl.Cys.OH	Benzonitrile	47	348
N.Cbzo.O-CH₃CO.L.Tyr.OH	H.L.Leu.OCH₃	THF†	76	191
	H.L.Leu.OCH₂C₆H₅	THF	61	191
(Cbzo)₂.L.Lys.OH	Cbzo↓ H.L.Lys.OCH₂C₆H₅	THF	48	191
	H.L.Tyr.OCH₃	THF	73	191
	H.L.Tyr.NH₂	THF	70	191
	Cbzo↓ H.L.Lys.OCH₃	Benzonitrile	62	190
Cbzo.Gly.OH	H.L.Lys.OC₃H₅	THF	71	191
	H.DL.Ala.Gly.OH	Benzonitrile	72	177, 197, 507, 538
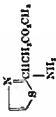
TABLE IX

ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.Gly.OH	H.DL.Ser.OCH₂C₆H₅	DMF*	69	69
	H.O-C₆H₅CH₂.DL.Ser.OC₂H₅	Chloroform	88	513
	H.L.Tyr.OC₂H₅	THF†	—	514
	H.NO₂.L.Arg.OC₂H₅	THF-methylene dichloride	59–71	216
C₆H₅CH₂SCO.Gly.OH	H.L.Arg.OCH₂C₆H₅	Acetonitrile-ethanol	66	515
	H.Gly.OC₂H₅	Chloroform	53, 74	443, 444
	H.DL.Phe.OC₂H₅	Chloroform	50, 70	443, 444
Tri.Gly.OH	H.L.Lys.OCH₃	Chloroform	68‡	12
Cbzo.DL.Ala.OH	H.im.C₆H₅CH₂.L.His.OCH₂C₆H₅	THF	60	227
	H.NO₂.L.Arg.OC₂H₅	THF-methylene dichloride	—	216
C₆H₅CH₂SCO.L.Ala.OH	H.Gly.OC₂H₅	Chloroform	37	443, 444
C₆H₅CH₂SCO.DL.Ala.OH	H.Gly.OC₂H₅	Chloroform	73	443, 444
Phth.L.Ala.OH	H.L.Pro.OCH₂C₆H₅	—	74	204
N-CH₃CO.DL.Ser.OH	H.L.Tyr.OCH₃	THF-water	40	516
Cbzo.L.Ser.OH	H.Gly.OC₂H₅	THF	50	204
Cbzo.DL.Ser.OH	H.Gly.OCH₂C₆H₅	DMF	72	69
Cbzo.L.Ser.OH	H.L.Tyr.OCH₃	Acetonitrile-dioxane	68	471
	H.L.His.OCH₃	THF	49	464
	H.im.C₆H₅CH₂.L.His.OCH₂C₆H₅	THF	57	227
Cbzo.DL.Ser.OH	H.NO₂.L.Arg.OC₂H₅	THF-methylene dichloride	—	216

TABLE IX—*Continued*

ANHYDRIDE FORMATION WITH N,N′-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
$\overset{NH_2}{\underset{|}{\text{Cbzo.L.Glu.OH}}}$	H.S.Bz.L.Cys.OCH₃	THF	76	87, 223
$\overset{NH_2}{\underset{|}{\text{Tri.L.Glu.OH}}}$	H.Gly.OCH₂C₆H₅	Methylene dichloride	>70	225
	H.L.Leu.OCH₂C₆H₅	Methylene dichloride	>70	225
	$\overset{NH_2}{\underset{|}{\text{H.L.Asp.OCH₂C₆H₅}}}$	Methylene dichloride	>70	225
(Tri)₂.L.Lys.OH	H.Gly.OC₂H₅	Methylene dichloride	92‡	12
	H.L.Glu(OC₂H₅)₂	Methylene dichloride	63‡	12
	Tri $\underset{|}{\text{H.L.Lys.OCH₃}}$	Methylene dichloride	—	12
(Cbzo)₂.L.His.OH	H.Gly.OCH₃	Chloroform	68	226
	H.O-C₆H₅CH₂.L.Ser.OCH₃	Chloroform	81	89, 226
	H.L.Thr.OCH₃	Chloroform	78	89, 226
	H.L.Leu.OCH₃	Chloroform	68	89, 226
	H.L.Met.OCH₃	Chloroform	85, 90	89, 226
	H.L.Glu(OC₂H₅)₂	Chloroform	70	89, 226
Cbzo.im.C₆H₅CH₂.L.His.OH	H.Gly.OCH₂C₆H₅	DMF	40	227
	H.L.Ser.OCH₂C₆H₅	DMF	60	227
	H.L.Leu.OCH₂C₆H₅	DMF	65	228
	H.L.Glu(OCH₂C₆H₅)₂	DMF	50	227
	H.im.C₆H₅CH₂.L.His.OCH₂C₆H₅	Methylene dichloride	54, 65	227, 228

Acyl / amine component	Yield, %	Solvent	References
(Try)$_3$.His.OH	80	Methylene dichloride	11
H.Leu.OCH$_3$	81	Methylene dichloride	11
H.Thr.OCH$_3$	85	Pyridine-acetonitrile	45
H.Arg.OCH$_3$	58	DMF	208
H.Try.OCH$_3$	92	Pyridine	45
Cbzo.Arg.OH			
$\quad$ NO$_2$			
H.Gly.OCH$_2$C$_6$H$_5$	54	THF-methylene dichloride	216
Cbzo.Arg.OH			
H.D.Ala.OCH$_2$C$_6$H$_5$	53	THF-methylene dichloride	216
H.D.Ser OC$_6$H$_5$	35	THF-methylene dichloride	216
H.D.Ser.OCH$_2$C$_6$H$_5$	53	THF-methylene dichloride	216
H.O.L.OCH$_2$C$_6$H$_5$	—	—	224
L·NCO.CH$_2$.NH(CH$_2$CH$_2$O)$_2$.CO$_2$H			
C$_6$H$_5$.CH(CH$_2$)$_2$.CH.CH$_2$.NH(CH(CO)CO$_2$H			
$\quad$ NH$_2$	1	THF	621
p.[(CCl$_3$)$_2$.N.C$_6$H$_4$.CH$_2$.CH$_2$.NHCH(NHCO)CO$_2$H]			
H.Gly.OC$_2$H$_5$	100	Chloroform	522
H.β.Ala.OC$_2$H$_5$	57	Chloroform	523
H.Val.OC$_2$H$_5$	59	Chloroform	523
H.Leu.OC$_2$H$_5$	40	Chloroform	623

Note: References 437 to 538 are on pp. 353–355.

† This is the yield of product after saponification.

TABLE IX—*Continued*

ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
p-(ClCH$_2$CH$_2$)$_2$NC$_6$H$_4$CH$_2$CH(NHCHO)CO$_2$H (*continued*)				
	H.Met.OC$_2$H$_5$	Chloroform	70	522
	H.Phe.OC$_2$H$_5$	Chloroform	73	523
	H.Try.OCH$_3$	Chloroform	47	523
	ClCH$_2$CH$_2$SCH$_2$CH(NH$_2$)CO$_2$C$_2$H$_5$	Chloroform	40	522
	C$_6$H$_5$CH$_2$SCH$_2$CH$_2$CH(NH$_2$)CO$_2$C$_2$H$_5$	Chloroform	100	522
Tri.Gly.OH	$\overset{\text{Tri}}{\overline{\quad}}$H.L.Lys.L.Glu(OC$_2H_5$)$_2$	Chloroform	46‡	12
Cbzo.L.Ser.OH	H.Gly.Gly.OCH$_2$C$_6$H$_5$	Chloroform-acetonitrile	56	215
	H.L.Tyr.L.Ser.OCH$_3$	DMF	56, 75	208, 471
Cbzo.L.Thr.OH	H.L.Val.L.Glu(OCH$_3$)$_2$	Chloroform	72	226
Cbzo.L.Try.OH	H.Gly.Gly.OC$_2$H$_5$	THF	—	514
Tri.L.Glu(OH)$_2$**	H.S.Tri.L.Cys.Gly.OC$_2$H$_5$	Methylene dichloride	75‡	519
$\overset{\text{NH}_2}{\overset{|}{\text{Cbzo.L.Glu.OH}}}$	$\overset{\text{NH}_2}{\overset{|}{\text{H.L.Asp.S.Bz.L.Cys.OCH}_3}}$ S.Bz.L.Cys.OCH$_2$C$_6$H$_5$	THF	78	87
Tos.L.Glu.OH	$\overset{\text{NH}_2}{\overset{|}{\text{H.L.Asp.NH}_2}}$	Dioxane	86	499
N-{4-(4'-CH$_3$OC$_6$H$_4$N=N)C$_6$H$_4$CH$_2$OCO]-N$^\omega$-Tos.L.Arg.OH	H.L.Try.Gly.OCH$_3$	—	—	47
Cbzo.Gly.Gly.OH	H.DL.Phe.OC$_2$H$_5$	Acetonitrile	86	149

Compound	Solvent	38	521
Cbzo.Val.Gly.OH	Dioxane	65	69
Cbzo.Gly.DL.Ser.OH	DMF	100 crude	511
Cbzo.Gly.L.Pro.OH	THF	160	205
S,N-(Tos)$_2$.L.Cys.L.Pro.OH	Methylene dichloride	66§	40
Phth.L.Val.L.Val.OH	Methylene dichloride	70	405
Cbzo.Leu.L.Val.OH	THF	04	231, 405
H.L.Glu(OCH$_3$)$_2$	Methylene dichloride	61	405
H.L.Glu(OCH$_3$)C$_4$H$_8$	Dioxane	32	521
Cbzo.Val.Leu.OH			
N$^{\alpha}$-Phenylalanyl-3-β-d-tetraacetyl-glucopyranosylcysteine			
Phth.Leu.L.Leu.OH	Methylene dichloride	83	46
Cbzo.Gly.L.Phe.OH	THF	87	204, 231
Phth.Thr.L.Phe.OH	Methylene dichloride	91	213
HCO.L.Val.L.Phe.OH	Methylene dichloride	92	213, 217
Cbzo.Val.Phe.OH	Dioxane-methylene dichloride	40	133
N$^{\alpha}$-Phenylalanyl-3-β-d-tetraacetyl-glucopyranosylcysteine	Dioxane	40	521
Cbzo.Gly.L.Try.OH	THF	—	514
Cbzo.L.Ser.L.Try.OH	Chloroform-acetonitrile	75	471
Cbzo.L.Val.L.Tyr.OH	—	66	230
S,N(Tos)$_2$.L.Cys.L.Tyr.OH	THF	02‡	500
H.L.Ileu.OCH$_3$	—		205
H.L.Ileu.OCH$_3$	THF	78	525
S.B$_2$.N.Tos.L.Cys.L.Tyr.OH	THF	91	87
H.L.Phe.OCH$_3$			

Note. References 437 to 538 are on pp. 353-355.

‡ This is the yield of product after saponification.
§ All the optical isomers were prepared.
** Only the γ-carboxyl group reacts.

TABLE IX—*Continued*

ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
Tos.L.Glu.L.Asp.OH (NH₂ NH₂ Cbzo)	H.S.Bz.L.Cys.OCH₂C₆H₅	DMF	40††	87, 223
Tri.Gly.L.Lys.OH	H.L.Lys.OCH₃	THF	—	208
Cbzo.O.C₆H₅CH₂.L.Ser.L.His.OH	H.L.Leu.OCH₃	Dioxane	08	513
Cbzo.L.Phe.*im*.C₆H₅CH₂.L.His.OH	H.L.Leu.OCH₃	DMF	50‡	227
	H.L.Asp(OCH₂C₆H₅)₂	DMF	74	227
Cbzo.L.Ser.OH	H.L.Leu.L.Val.L.Glu(OC₂H₅)₂	Methylene dichloride	57	465
Cbzo.S.Bz.L.Cys.OH	H.L.Pro.L.Lys.Gly.OC₂H₅ (Tos)	THF	81	404, 505
4-(4-OH₃OC₆H₄N=N)C₆H₄CH₂OCO.L.Phe.OH	H(Nᵃ-Tos).L.Arg.L.Try.Gly.OCH₃	—	—	47
(Cbzo)₂.L.His.OH	H.L.Thr.L.Val.L.Glu(OOH₃)₂	DMF	90	226
H₂NCNHOH₂CO₂H (NH)	H₂N—[ring]—CONH—[ring]—CONHCH₂CONH₂	—	30	95

Acyl component	Amino component	Solvent	Yield	References
Cbzo.L-Pro.L-Phe.OH	H.L.His.L.Leu.OCH₃	Ethyl acetate-acetonitrile	61	230
(Trt)₂.L-His.L-Phe.OH	H.L.Arg.L.Tyr.OCH₃ NH₂	DMF	69, 89	45, 208
Trt.L-Leu.O.C₆H₄CH₂.L-Tyr.OH	H.L.Glu.L.Leu.OCH₃	DMF	76	222
Cbzo.S.Bz.L-Cys.L-Tyr.OH (Cbzo)	H.L.Tyr.L.Ileu.OCH₃	DMF-acetonitrile	65	218
Trt.Gly.L-Lys.OH (NH₂ NO₂)	H.L.Pro.L.Val.OCH₃	THF	93	45, 208
Cbzo.L-Asp.L-Arg OH (NH₂)	H.L.Val.L.Tyr.OCH₃	DMF	83	461
Cbzo.L-Arg.L-Arg.OH	Ileu.Pro.L.Val.OCH₃	Methylene dichloride	57	208
S.N.(Trt)₂.L-Cys.L-Pro.L-Leu.OH	H.Gly.OCH₃	Methylene dichloride	98	205
Path L-Leu.L-Leu.L-Leu.OH	R.L-Leu.OCH₃		86	40
Trt.L-Asp.OH (NH₂)		Methylene dichloride	96	225
Nα-[4-[4-CH₃.O.C₆H₄.N=N]₂.C₆H₃.CO₂]-γ-C₆H₄CH₂.L-His.OH	H.S.Trt.L.Cys.L.Pro.L.Leu.Gly.OH / H.L.Phe[S-Trt].L.Arg.L.Try.Gly.OCH₃	—	—	—
Cbzo O C₆H₄CH₂.L-Ser.L-His.OH	H.L.Leu.L.Val.L.Glu(OC₂H₅)₄	Dioxane	82	47, 234

Note: References 497 to 538 are on pp 353-355.

‡ This is the yield after saponification.

†† A 15% yield of 'anhydro' compound was obtained, presumably due to dehydration of the asparagine amide group.

TABLE IX—Continued

ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
Cbzo.L.His.L.Phe.L.Arg.OH (NO$_2$)	H.L.Try.Gly.OCH$_2$C$_6$H$_5$	DMF	86‡‡	44
Tri.L.Glu.OH (NH$_2$)	H.L.Asp.S.Tri.L.Cys.L.Pro.L.Leu.Gly.OCH$_3$ (NH$_2$)	Methylene dichloride	72	225
Cbzo.L.Val.L.Tyr.OH	H.L.Val.L.His.L.Pro.L.Phe.OCH$_3$	Ethyl acetate	74	526
Cbzo.S.Bz.L.Cys.L.Tyr.OH (OCH$_3$ OCH$_3$)	H.L.Ileu.L.Glu.L.Asp.S.Bz.L.Cys.NH$_2$ (NH$_2$ NH$_2$)	—	—	527
Tri.L.Glu.L.Asp.OH	H.S.Tri.L.Cys.L.Pro.L.Leu.Gly.OCH$_3$	Methylene dichloride	72	205
Cbzo.Gly.Gly.DL.Phe.OH	H.Gly.Gly.DL.Phe.OC$_2$H$_5$	DMF	<66	149
H.Gly.DL.Val.Gly.Gly.DL.Val.Gly.OH§§		Methanol-water	45	483
H.Gly.Leu.Gly.Gly.Leu.Gly.OH§§		Methanol-water	47	242
Tri.Gly.L.Lys.L.Lys.OH (Cbzo Cbzo)	H.L.Arg.L.Arg.L.Pro.L.Val.OCH$_3$	DMF	45	208
Cbzo.L.Asp.L.Arg.OH (NH$_2$ NH$_2$)	H.L.Val.L.Tyr.L.Val.L.His.L.Pro.L.Phe.OCH$_3$	DMF	61	526

	Chao			
(Tos)L.His.L.Phe.L.Arg.L.Try.OH	H.Gly.L.Lys.L.Pro.L.Val.NH₂	DMF-acetonitrile	83	45
Cbzo.L.Val.L.Tyr.L.Val.L.His.OH / NO₂	H.Pro.L.Phe.L.His L.Leu.OCH₃ / Tos	DMF	51	230
Cbzo.L.His.L.Phe.L.Arg.L.Try.Gly.OH / NH₂ NH₂	H.L.Lys.L.Pro.L.Val.NH₂ / Tos		—	528
Tos.S.Bz.L.Cys.L.Tyr.L.Phe.L.Glu L.Asp.OH		THF	42	85, 505
	H.S.Bz.L.Cys L.Pro.L.Lys.NH₂ / NH₂ NH₂			
Cbzo.S.Bz.L.Cys.L.Tyr.L.Val.OH	H.L.Glu L.Asp.S.Bz.L.Cys.L.Pro.L.Leu.Gly.NH₂ / DMF		—	403
	NH₂			
L.Asp.S.Bz.L.Cys.L.Pro.L.Leu.NH₂	H.L.Glu.NH₂	THF	64	500
Cbzo.S.Bz.L.Cys.L.Tyr.L.Ileu.OH	NH₂ S.Bz.L.Cys.L.Pro.L.Leu.Gly.NH₂ / H.L.Glu.L.Asp.NH₂	THF-water	73	490

Note: References 457 to 528 are on pp. 353-355.

‡‡ The product was partially racemized; a 19% yield of the L isomer was obtained.

§§ The product is the cyclohexapeptide.

TABLE IX—*Continued*

ANHYDRIDE FORMATION WITH N,N'-DICYCLOHEXYLCARBODIMIDE

Acid	Amine	Solvent	Yield, %	Refs.
S,N-(Tri)$_2$.L.Cys.L.Tyr.L.Ileu.OH	OCH$_3$ OCH$_3$ ┘ ┘ H.L.Glu.L.Asp.S.Tri.L.Cys.L.Pro.L.Leu.Gly.OCH$_3$	Methylene dichloride	75	205
Cbzo.S.Bz.L.Cys.L.Phe.L.Ileu.L.Glu.L.Asp.OH	NH$_2$ NH$_2$ ┘ ┘ H.S.Bz.L.Cys.L.Pro.L.Leu.Gly.NH$_2$	—	—	504
Cbzo.L.Asp.L.Arg.OH NH$_2$ NO$_2$ ┘ ┘ Tos	Tos ┘ H.L.Val.L.Tyr.L.Val.L.His.L.Pro.L.Phe.L.His.L.Leu.OCH$_3$	—	70	230
Tri.L.Val.L.Lys.L.Leu.D.Phe.L.Pro.OH Cbzo ┘	Cbzo Cbzo ┘ ┘ H.L.Val.L.Lys.L.Leu.D.Phe.L.Pro.OCH$_3$	Acetonitrile	95	529
Tri.Gly.L.Lys.L.Pro.L.Val.OH Cbzo ┘	Cbzo Cbzo ┘ ┘ H.Gly.L.Lys.L.Lys.L.Arg.L.Arg.L.Pro.L.Val.OCH$_3$	DMF	49	208
(Tri)$_2$.L.His.L.Phe.L.Arg.L.Try.OH	Cbzo Cbzo ┘ ┘ H.Gly.L.Lys.L.Pro.L.Val.Gly.L.Lys.L.Lys.L.Arg.L.Arg.L.Pro.L.Val.OCH$_3$	DMF	73	208
Cbzo.L.Ser.L.Tyr.L.Ser.L.Met.L.Glu.OH OCH$_2$C$_6$H$_5$ ┘	Cbzo Cbzo ┘ ┘ H.L.His.L.Phe.L.Arg.L.Try.Gly.L.Lys.L.Pro.L.Val.Gly.L.Lys.L.Lys.L.Lys.L.Arg.L.-Arg.L.Pro.L.Val.OCH$_3$	DMF	77	208

Note: References 437 to 538 are on pp. 353–355.

TABLE X

ANHYDRIDE FORMATION WITH MISCELLANEOUS CARBODIIMIDES

Acid	Amine	Solvent	Yield, %	Ref.
A. 1-Cyclohexyl-3-(2-diethylaminoethyl)carbodiimide				
Phth.L.Phe.OH	H.Gly.OC$_2$H$_5$	Dioxane	20	233
Phth.Gly.OH	H.Gly.OC$_2$H$_5$	Water	75	233
B. 1-Cyclohexyl-3-(4-diethylaminocyclohexyl)carbodiimide Meth-p-toluenesulfonate				
Phth.L.Phe.OH	H.L.Leu.OC$_2$H$_5$	Acetonitrile	60	233
C. 1-Cyclohexyl-3-(2-morpholinoethyl)-4-ethylcarbodiimide Meth-p-toluenesulfonate				
Phth.L.Phe.OH	H.Gly.OCH$_3$	Methylene dichloride	83	32
D. 1-Cyclohexyl-3-(4-diethylaminocyclohexyl)carbodiimide				
(±) structure	H.Gly.OC$_2$H$_5$	Acetonitrile	83	233
Cbzo.Gly.L.Phe.OH				
Phth.L.Phe OH	H.Gly.OC$_2$H$_5$	Dioxan	90	233
Phth.L.Phe.OH	H.Gly.OC$_2$H$_5$	Dioxane–water (3:1)	71	233
Phth.L.Phe.OH	H.L.Leu.OC$_2$H$_5$	Dioxane	87	233
Phth.L.Phe.OH	H.L.Leu.OC$_2$H$_5$	Dioxane–water (5:2)	50	233
Phth.L.Phe.OH	H.Phe.OCH$_3$	Dioxane	88	233
Cbzo.Gly.L.Phe.OH	H.Gly.OC$_2$H$_5$	Dioxane	81	233

Note: References 437 to 538 are on pp. 353–355.

TABLE X—*Continued*

ANHYDRIDE FORMATION WITH MISCELLANEOUS CARBODIIMIDES

Acid	Amine	Solvent	Yield, %	Ref.
E. 1-Cyclohexyl-3-[2-morpholinyl-(4)-ethyl]carbodiimide				
Cbzo.L.Val.OH	H.L.His.OCH₃	Acetonitrile	77	230
Phth.L.Phe.OH	H.Gly.OC₂H₅	Dioxane	81	233
Cbzo.L.Val.L.Tyr.OH	H.L.Val.L.His.OCH₃	Acetonitrile	65	230
Cbzo.L.Val.L.Tyr.L.Val.OH	H.L.His.OCH₃	THF*	50	230
Cbzo.L.Val.L.Tyr.L.Val.L.His.OH	H.L.Pro.L.Phe.OCH₃	DMF†	58	526
Cbzo.L.Asp.L.Arg.L.Val.L.Tyr.OH [NH₂] [NO₂]	H.L.Ileu.L.His.L.Pro.L.Phe.OCH₃	DMF	22	401
Tri.L.Val.L.Orn.L.Leu.D.Phe.L.Pro.OH [Tos]	H.L.Val.L.Orn.L.Leu.D.Phe.L.Pro.OCH₃ [Tos]	Ethyl acetate	80	280

Note: References 437 to 538 are on pp. 353–355.

* THF is tetrahydrofuran.
† DMF is dimethylformamide.

TABLE XI

ANHYDRIDE FORMATION WITH KETENIMINES

Acid	Amine	Solvent	Yield, %	References
A. Diphenylketene-p-tolylamine				
Cbzo.Gly.OH	H₂L.Thr.OC₂H₄	Benzene	—	247
Phth.Gly.OH	H₂L.Try.OCH₃	Benzene	—	247
	H.Gly.OC₂H₄	Benzene	54	244, 246, 247
	H L.Leu.OC₂H₅	Benzene	28*	244, 247
Phth.βAla.OH	p-H₂NC₆H₄.CO₂C₂H₅	Methylene dichloride	77	244, 246, 247
Cbzo.S.Bzl.Cys.OH	H₂O.OC₂H₅	Benzene	32†	247
Phth.L.Phe OH	H₂L.Tyr.OC₂H₄	Methylene dichloride	—	244, 246
NH₂	H₂L.Leu.OC₂H₄	Benzene	—	247
Cbzo.Asp.OH	H.S.Bn.L.Cys.OH	THF‡	45	244
Phth.Gly.OH	H.Gly.Gly.OC₂H₅	Benzene-methylene dichloride	45	244, 247
B. Ethyl-α-butylketene-n-butylamine				
Cbzo.Gly.OH	H.Met.OC₂H₅	Methylene dichloride	—	247
Phth.Gly.OH	H.Gly OC₂H₅	Benzene or ethanol-water	—	247

Note: References 437 to 538 are on pp. 353–355.

* This is the yield of acyl peptide.
† This is the yield of product obtained upon saponification.
‡ THF is tetrahydrofuran.

TABLE XII

ANHYDRIDE FORMATION WITH ACETYLENIC ETHERS

Acid	Amino	Solvent	Yield, %	References
A. Methyl Ethinyl Ether				
Cbzo.Gly.OH	H.Gly.OC$_2$H$_5$	Nitromethane	75	255, 265, 266
	H.L.Phe.OCH$_2$C$_6$H$_5$	Ethyl acetate	90	265, 266, 530
	H.DL.Ser.OC$_2$H$_5$	DMF*	60	265, 266, 530
(C$_6$H$_5$CH$_2$)$_2$.Gly.OH	H.L.Pro.OCH$_2$C$_6$H$_5$	Methylene dichloride	—	265, 266, 530
Phth.L.Ala.OH	H.Gly.OC$_2$H$_5$	None	70	255, 265, 266, 530
Cbzo.L.Leu.OH	H.Gly.OC$_2$H$_5$	Ether	60	265, 266, 530
Tos.L.Ileu.OH				
OH │ Cbzo.L.Glu.OC$_2$H$_5$	H.S.Bz.L.Cys.Gly.OC$_2$H$_5$	None	70	265, 266, 530
B. Ethyl Ethinyl Ether				
Phth.Gly.OH	H.Gly.OC$_2$H$_5$	Dioxane	80†	258
Tri.DL.Ala.OH	H.DL.Try.OCH$_3$	None	80	265, 266, 530, 531
Cbzo.S.Bz.L.Cys.OH	H.Gly.OC$_2$H$_5$	Ethyl acetate	90	265, 266, 530
Phth.L.Phe.OH	H.Gly.OC$_2$H$_5$	Chloroform	60	258
Cbzo.Gly.L.Phe.OH	H.Gly.OC$_2$H$_5$	None	40	258
H.Gly.Leu.Gly.Gly.Leu.Gly.OH‡	H.Gly.OC$_2$H$_5$	Methanol	11	242

Note: References 437 to 538 are on pp. 353-355.

* DMF is dimethylformamide.

† The yield is based on the adduct of phthaloylglycine with ethoxyacetylene.

‡ The product was a cyclo-hexapeptide.

TABLE XIII

ANHYDRIDE FORMATION WITH ETHYL α-CHLOROETHYL ESTER AND WITH α,α'-DICHLORODIETHYL ETHER

Acid	Amine	Solvent	Yield, %	References
A. Ethyl α-Chloroethyl Ether				
Cbzo.Gly.OH	H.Gly.OC₂H₅	Ethyl acetate	61	207
Phth Gly.OH	H.Gly.OC₂H₅	Ethyl acetate	85	207
	H.Gly.OC₂H₅	Ethyl acetate	42	207
	H.L.Phe.OC₂H₅	Ethyl acetate	54	207
	H.Gly.OC₂H₅	Ethyl acetate	51	207
Cbzo.L Ala.OH	H.Gly.OC₂H₅	Ethyl acetate	50	207
	H.L.Phe.OC₂H₅	Ethyl acetate	20	207
Phth.L Ala.OH	H.Gly.OC₂H₅	Ethyl acetate	62	207
Cbzo L Val.OH	H.Gly.OC₂H₅	Ethyl acetate	60	207
Cbzo.L Leu.OH	H.Gly.OC₂H₅	Ethyl acetate	51	207
	H.L.Phe.OC₂H₅	Ethyl acetate	75	207
Phth.L.Leu.OH	H.Gly.OC₂H₅	None	85	207
	H.Gly.OC₂H₅	Ethyl acetate	83	207
Phth.L Phe.OH	H.Gly.OC₂H₅	Ethyl acetate	70	207
Cbzo.Gly.OH	H.Gly.OC₂H₅	Ethyl acetate	25	207
Phth.Gly.OH	H.Gly.Gly.OC₂H₅	None	56	207
	H.Gly.Gly.Gly.OC₂H₅			
B. α,α'-Dichlorodiethyl Ether				
Cbzo.Gly.OH	H.Gly.OC₂H₅	Ethyl acetate	71	207
Phth.Gly.OH	H.Gly.OC₂H₅	Ethyl acetate	90	207
	H.S.Bu.L.Ala.OH	Ethyl acetate	92	207
Cbzo L Ala.OH	H.Gly.OC₂H₅	Ethyl acetate	61	207
Cbzo.L Phe.OH	H.Gly.OC₂H₅	Ethyl acetate	53	207
Phth.Gly.OH	H.Gly.OC₂H₅	Ethyl acetate	83	207
	H.Gly.Gly.OC₂H₅	None	61	207
	H.Gly.Gly.Gly.OC₂H₅	None	38	207

TABLE XIV

ANHYDRIDE FORMATION WITH p-NITROPHENOL

(All yields are based upon the p-nitrophenyl ester.)

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.Gly.OH	Ethanol-water	90	38
	H.Gly.OC₂H₅	Ethanol	94	38
	H.L.Phe.OH	Dioxane-water	32	38
Phth.Gly.OH	H.Gly.OH	DMF-water*	72	269
	H.Gly.OC₂H₅	Ethyl acetate	96†	283
	H.L.Ala.OC₂H₅	THF‡	43	269
	H.L.Tyr.OC₂H₅	THF	71	269
	NH₂ | H.L.Asp.OH	Dioxane-water	64	283
Cbzo.L.Val.OH	H.L.Tyr.OC₂H₅	THF	67	230
	H.O.C₆H₅CO.L.Tyr.OC₂H₅	Ethyl acetate	95	230
	Tos | H.L.Lys.OCH₃	—	67	529
	Tos | H.L.Orn.OCH₃	THF	67	280
Cbzo.L.Leu.OH	H.D.Phe.OC₂H₅	THF	96	280
Phth.D.Leu.OH	H.Gly.NH₂	DMF	93	283

				References
Cbzo.S.Bz.L.Cys.OH	H.L.Phe.OCH₃, H.L.Tyr.OH, H.L.Tyr.OC₄H₉	THF-water, THF	— / 9 / 83§	504 / 209 / 200, 532
OCH₃ Cbzo.L.Asp.OH	H.L.Arg.OH	—	—	272
OCH₃ OC₄H₉ Cbzo.L.Asp.L.Arg.OH	H.L.Val.OH	—	—	272
Cbzo.S.Bz.L.Cys.OH Cbzo.L.Val.L.Tyr.L.Val.OH	H.L.Pro.L.Leu.Gly.OC₄H₉, H.L.His OH	Ethyl acetate	—	283 / 272
H.Gly.L.Leu.Gly.OH‖		DMF-pyridine	20	140
H.Gly.L.Phe.Gly.OH‖		DMF-pyridine	29–38	140
H(Gly.L Leu Gly)₂OH‖		DMF-pyridine	08	146 / 146
Tos H[L.Val.L.Lys.L.Leu.L.Phe.L.Pro]₂OH‖		DMF-pyridine	21	148, 281, 529
Tos Tfl[L.Val.L.Orn.L.Leu.D.Phe.L.Pro]OH‖		DMF-pyridine	23**	148, 278–280

Note: References 437 to 558 are on pp. 353–355.

* DMF is dimethylformamide.
† Lower yields were obtained in other solvents.
‡ THF is tetrahydrofuran.
§ This is the yield after hydrolysis.
‖ The product is a cyclo-hexapeptide.
¶ The product is a diketo cyclo-decapeptide.
** This is the over-all yield of dioxyl Gramicidin S.

TABLE XV

ANHYDRIDE FORMATION WITH MISCELLANEOUS PHENOLS

(All yields are based upon the phenyl ester.)

Phenol	Acid	Amine	Solvent	Yield, %	Reference
HOC_6H_5	Phth.Gly.OH	H.Gly.OC$_2$H$_5$	Benzene	3	208
$HOC_6H_4NO_2$-m	Phth.Gly.OH	H.Gly.OC$_2$H$_5$	Benzene	86	209
	Cbze.S.Bz.L.Cys.OH	H.L.Tyr.OC$_2$H$_6$	THF*	74†	209
	Phth.Gly.OH	H.Gly.OC$_2$H$_5$	Dioxane	60	209
$HOC_6H_3(NO_2)_2$-2,4	H.Gly.DL.Phe.Gly.OH‡		DMF-pyridine§	40–46	149
$HOC_6H_4SO_2CH_3$-p	H.Gly.Gly.DL.Phe.OH‡		DMF-pyridine	25	149
	H(Gly.Gly.DL.Phe)$_2$.OH‡		DMF-pyridine	13	149

Note: References 437 to 538 are on pp. 353–355.

* THF is tetrahydrofuran.
† This is the yield after hydrolysis.
‡ DMF is dimethylformamide.
§ The product is the cyclo-hexapeptide.

TABLE XVI

Boissonnas's Method

$$\underset{\text{YCOCHR}_1\text{NH}_2}{\overset{}{\bigcirc}}\underset{\text{CONHCHR}_1\text{CO}_2\text{X}}{}$$

Y	$H_2NCHR_1CO_2H$	$H_2NCHR_1CO_2X$	Solvent	Yield, %	References
O	H.Gly·OH	H.L.Phe.OCH₃	Chloroform	Moderate	293–295
O	H.L.Phe.OH	H.Gly.OCH₃	Chloroform	100	293, 294
O	H.DL.Phe.OH	H.Gly.OCH₃	THF-methanol*	95	288, 293–295
O	H.Gly·OH	H.L.Phe.Gly.OCH₃	Methanol	100	293, 294
O	H.Gly·OH	H.DL.Phe.Gly.OCH₃	Methanol	95	288, 293–295
O	H.DL.Phe.OH	H.DL.L.Phe.Gly.OCH₃	Various	—	293–295
S	H.DL.Phe.OH	H.Gly.NHC₄H₉	Chloroform	—	294, 295

Note: References 437 to 508 are on pp. 353–355.

* THF is tetrahydrofuran.

TABLE XVII

ANHYDRIDE FORMATION WITH CHLOROACETONITRILE

Acid	Amino	Solvent	Yield, %	References
$F_3CCO.Gly.OH$	$H.Gly.OC_2H_5$	Ethyl acetate	90	320
$C_6H_5CO.Gly.OH$	$H.Gly.OH$	DMF-water*	70	318
	$H.Gly.OC_2H_5$	Ethyl acetate	91	304, 316
	$H.L.Leu.OC_2H_5$	Ethyl acetate	81–90	304, 316
	$H.L.Tyr.OC_2H_5$	Ethyl acetate	ca. 90	304, 318
	$H.O-C_6H_5CO.L.Tyr.OC_2H_5$	Ethyl acetate	100	304, 318
	$H.L.Leu.OC_2H_5$	THF†	98	146
$Cbzo.Gly.OH$	$H.DL.Met.OH$	Acetonitrile-water	80	316
	$H.Phe.OCH_3$	Chloroform	85	314
	$H.L.Glu(OC_2H_5)_2$	Chloroform	81	317
	$H.L.Glu(OC_2H_5)_2$	Chloroform	57	317
$p-NO_2.Cbzo.Gly.OH$	$H.Gly.OC_2H_5$	THF	97	312
$Trt.Gly.OH$	$H.Gly.OC_2H_5$	Ethyl acetate	89	320
$F_3CCO.L.Ala.OH$	$H.Gly.OC_2H_5$	Ethyl acetate	90	320
$F_3CCO.DL.Ala.OH$	$H.L.Ala.OC_2H_5$	Ethyl acetate	82	320
$F_3CCO.L.Ala.OH$	$H.L.Ala.OC_2H_5$	Ethyl acetate	80	320
$F_3CCO.L.Ala.OH$	$H.DL.Ala.OC_2H_5$	Ethyl acetate	67	320
$F_3CCO.DL.Ala.OH$	$H.Gly.OC_2H_5$	Ethyl acetate	80	320
$F_3CCO.DL.Pro.OH$	$H.Gly.OC_2H_5$	Ethyl acetate	84	320
$F_3CCO.L.Val.OH$	$H.Ala.OC_2H_5$	Ethyl acetate	82	316, 318
$Cbzo.L.Leu.OH$	$H.Gly.OC_2H_5$	Ethyl acetate	75	316, 318
$Cbzo.DL.Leu.OH$	$H.Gly.OC_2H_5$	Ethyl acetate	85	316, 318
$p-NO_2.Cbzo.DL.Leu.OH$	$H.Gly.OC_2H_5$	Acetonitrile	78	304, 316
$Cbzo.S.Bz.L.Cys.OH$	$H.Gly.NH_2$	Ethyl acetate	74	311
	$H.Gly.OC_2H_5$	THF†	70	311
$Tos.DL.Met.OH$	$H.L.Tyr.OC_2H_5$	Ethyl acetate	88	316
$F_3CCO.DL.Phe.OH$	$H.O-C_6H_5CO.L.Tyr.OC_2H_5$	Ethyl acetate	78	320
	$H.Gly.OC_2H_5$	Ethyl acetate	81	320
$Cbzo.Phe.OH$	$H.Gly.OH$	Chloroform	64	314
$Cbzo.DL.Phe.OH$	$H.Gly.OC_2H_5$	THF†	86	149

47

Acyl component	Amino component	Solvent	Yield (%)	References
Cbz.L.Try.OH	H.Gly.OCH$_3$	Ethyl acetate	94	304, 316
O,N·(Cbz)$_2$.L.Try.OH	H.Gly.OC$_2$H$_5$	Ethyl acetate	71	304, 316
	H.D.L.Leu.OC$_2$H$_5$	Ethyl acetate	>60	311
Tos.L.Glu.OH	H.Gly.OH	Ethyl acetate	72·00	301, 310
C$_4$H$_7$.CO.Gly.OH	H.L.Leu.Gly.OC$_2$H$_5$	Ethyl acetate	92	310, 318
	H.D.L.Leu.NH$_2$	Acetonitrile	85	310, 318
Cbz.Gly.OH	H.Gly.OH	Acetonitrile–water	80	316
Trp.OH	H.Phe.Gly.OC$_2$H$_5$	THF	79	149
K$_2$CO$_3$.L.Ala.OH	H.Pro.Gly.OC$_2$H$_5$	THF	60	149
Cbz·S Bz.L.Cys.OH	H.L.Ala.Ala.OC$_2$H$_5$	Ethyl acetate	83	149
Cbz.L.Phe.OH	H.Leu.Phe.Gly.OC$_2$H$_5$	Ethyl acetate	43	320
Tri.Gly.Gly.OH	H.O.tetrahydropyranyl.L.Tyr.L.Ileu.OC$_2$H$_5$	Ethyl acetate	53	311
Cbz.Gly.L.Leu.OH	H.L.Tyr.L.Ileu.OC$_2$H$_5$	Chloroform	>41	311
Cbz.Ala.L.Leu.L.Phe.OH	H.Gly.Leu.OCH$_3$	THF	>80	314
Cbz.δ.L.Glu.L.Cys.L.Try.OH	H.Gly.OC$_2$H$_5$	THF	65	312
Cbz.α.Gly.OH	H.L.Leu.OC$_2$H$_5$	THF	97	146
	H.L.Phe.OC$_2$H$_5$	Ethyl acetate	58	280
K$_2$CO$_3$.Gly.Gly.Gly.OH	H.Gly.OC$_2$H$_5$	THF	80	306, 311
Tri.Gly.Gly.OH	H.Gly.OC$_2$H$_5$	Ethyl acetate	81	312
Cbz O,N·L.Ala Gly.OH	H.Gly.OC$_2$H$_5$ OCCl$_3$	THF	>60	320
Cbz2 Gly.L.Leu Gly.OH‡	H.Gly.OC$_2$H$_5$	Acetonitrile	98	312
H.Gly.L.Phe Gly.OH	H.Gly.OCH$_3$	Pyridine	13	304, 316
H.Gly.DL.Phe Gly.OH§	H.Gly.L.Leu.Gly.OH§	THF	70	146
		DMF–pyridine	33	312, 313
		DMF–pyridine	20	149

Note: References 437 to 538 are on pp. 353–355.

* DMF is dimethylformamide.
† THF is tetrahydrofuran.
‡ The product is a cyclo-tetrapeptide.
§ The product is a cyclo-hexapeptide.

TABLE XVIII

ANHYDRIDE FORMATION WITH MISCELLANEOUS ESTERS

Reagent	Acid	Amine	Solvent	Yield, %	Reference
$BrCH_2CO_2C_2H_5$	Cbzo.Gly.OH	H.Gly.Gly.OH	Acetonitrile-water	40	316
	$C_6H_5CONHCHOHCO_2H$	H.Gly.OC_2H_5	Acetonitrile	56	322
$BrCH(CO_2C_2H_5)_2$	$C_6H_5CO.Gly.OH$	$H.O.C_6H_5CO.L.Tyr.OC_2H_5$	Ethyl acetate	65	316
$BrCH_2C \equiv CH$	Phth.Gly.OH	H.Gly.OC_2H_5	Ethyl acetate	—	310
$IMgOCH_2CH_3$	$F_3CCO.Gly.OH$	H.Gly.OC_2H_5	Ethyl acetate	94	320

Note: References 437 to 538 are on pp. 353–355.

TABLE XIX

ANHYDRIDE FORMATION WITH ACYLIMIDAZOLES (im-ACYL-L-HISTIDINE METHYL ESTER)

Starting Compound	Amine	Product	Yield, %	Reference
im-Hippuryl-N-benzoyl-L-His.OCH_3	H.Gly.OH	$C_6H_5CO.Gly.Gly.OH$	35	325
im-N-(Cbzo.Gly)_2.L.His.OCH_3	H.Ala.OCH_3	Cbzo.Gly.Ala.OCH_3	30	229

Note: References 437 to 538 are on pp. 353–355.

TABLE XX

ANHYDRIDE FORMATION WITH N,N'-CARBONYLDIIMIDAZOLE

Acid	Amine	Solvent	Yield, %	Reference
Cbzo.Gly.OH	H L.Leu OC₂H₅	THF*	>68	338
	H L.Phe.OH	THF	40	339
	H L.Tyr.OC₂H₅	THF	83	328
Cbzo.Ala OH	H.Gly.OC₂H₅	THF	65	328
(CH₃)₃COCO.L.Phe.OH	H.Gly.OC₂H₅	THF	78	328
Cbzo Gly.L.Phe.OH	H L Gly OC₂H₅	DMF†	87	328

Note. References 437 to 638 are on pp. 353–356.

* THF is tetrahydrofuran.
† DMF is dimethylformamide.

TABLE XXI

ANHYDRIDE FORMATION WITH 3,5-DIMETHYLPYRAZOLE

Acylpyrazole	Amine	Solvent	Yield, %	Reference
Tos Gly.OH	H.DL.Ala.OC₂H₅	None	80	332
Tos DL.Ala.OH	H.DL.Ala.OC₂H₅	None	75	332
Tos.Gly.DL.Ala.OH	H DL.Val.OC₂H₅	—	58	332

Note. References 437 to 638 are on pp. 353–356.

TABLE XXII

ANHYDRIDE FORMATION WITH THIOPHENYL ESTERS

A. Thiophenyl Esters

Acid	Amine	Solvent	Yield, %	References
F₃CCO.Gly.OH	H.DL.Phe.OH	THF-water*	14	533
Cbzo.Gly.OH	H.Gly.OH	—	75	338
	H.DL.Ala.OH	Methanol	90	336, 347, 361
	H.DL.Ala.OH	THF-water	75	336
	H.L.Pro.OH	THF-methanol-water	68 crude	59
	H.DL.Pro.OH	THF-methanol-water	80	59
	H.S.Bz.L.Cys.OH	THF-water	—	348
	H.DL.Phe.OH	THF-water	75	336
Cbzo.β.Ala.OH	H.β.Ala.OH	Methanol-water	70	336
Cbzo.S.Bz.L.Cys.OH	H.Gly.OH	THF-water	69	348
Cbzo.DL.Try.OH	H.S.Bz.L.Cys.OH	THF-water	100	348
Tos.β.Ala.OH	H.Gly.OH	—	75	338
Cbzo.S.Bz.L.Cys.OH	H.β.Ala.β.Ala.OH	Methanol-water	—	347
Cbzo.Gly.Gly.OH	H.Gly.Gly.OH	THF-water	31	348
	H.L.Pro.OH	THF-methanol-water	82 crude	59
Cbzo.S.Bz.L.Cys.Gly.OH	H.S.Bz.L.Cys.OH	THF-water	78	348
Cbzo.Gly.L.Leu.OH	H.S.Bz.L.Cys.OH	THF-water	21	348
Cbzo.Gly.DL.Phe.OH	H.Gly.OH	THF-methanol-water	70	37
Cbzo.Gly.Gly.OH	H.DL.Ala.OH	THF-water	70	336
H.Gly.DL.Val.DL.Ala.Gly.DL.Val.DL.Ala.OH†	H.Gly.L.Pro.OH	THF-methanol-water	100 crude	59
		DMF-pyridine‡	18	37

B. p-Nitrothiophenyl Esters

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.L.Phe.OH	Dioxane-water	93	38
	H.DL.Phe.OH	Dioxane-water	90	38

Cbzo.Leu.OH	H.Gly.OH	THF-water	98	38, cf. 349
Cbzo.Gly.OH	H.L.Leu.Gly.OH	THF-water	93	38
Cbzo.Gly.L.Phe.OH	H.Gly.OH	Dioxane-water	100	38, 335
	H.Gly.OC$_2$H$_5$	DMF	96	38
Cbzo.Gly.L.Ala.OH	H.L.Phe.Gly.OH	Dioxane-water	55 l.l.	38
			21 pt.	
Cbzo.Gly.L.Leu.Gly.OH	H.L.Leu.Gly.OH	THF	93 crude	38, cf. 340
H.Gly.L.Leu Gly.L.Leu Gly.OH‡		Water	41–44	334, 319
Cbzo.Gly.L.Leu.Gly.OH§		Water	11.5	340
	H.Gly.L.Leu.Gly.OH	THF	—	340
Cbzo Gly.L.Leu.Gly.L.Leu.Gly.O[H]¶	H.Gly.L.Leu.Gly.OH	Water	20	340

Note: References 437 to 538 are on pp. 354–355.

* THF is tetrahydrofuran.
† DMF is dimethylformamide.
‡ The product was a cyclo-hexapeptide.
§ The product was a cyclo-peptide.
¶ A cyclo hexapeptide was formed upon hydrogenolysis.

TABLE XXIII

ANHYDRIDE FORMATION WITH MISCELLANEOUS THIOL COMPOUNDS

Thiol	Acid	Amine	Solvent	Yield, %	References
H_2S	$C_6H_5CO.Gly.OH$	H.dl.Ala.OH	DMF*	70	340
	Phth.Gly.OH	H.Gly.OCH₃	Methylene dichloride	—	339
	Benzalglycine	H.Gly.OH	Water	20	346
$HSCH_3$	Cbzo.Gly.OH	H.dl.Val.OH	Methylene dichloride	—	347, 361
$HSCH_2CO_2H$	$C_6H_5CO.Gly.OH$	H.Gly.OH	—	46†	271, 344, 363
	Cbzo.Gly.OH	H.Gly.OH	—	70	271, 344
	Cbzo.Gly.OH	H.dl.Met.OH	—	60	271, 344
	Cbzo.Gly.OH	H.Gly.Gly.OH	—	70	271, 344
	Cbzo.Gly.OH	H.dl.Ala.Gly.OH	—	73	271, 344
	H.Gly.Gly.Gly.OH‡		Pyridine	13	312
	H.Gly.Gly.Gly.OH‡		DMF-pyridine	69	312
$o\text{-}HSC_6H_4CO_2H$	Cbzo.Gly.OH	H.Gly.OH	—	40	271, 344
	$C_6H_5CO.Gly.OH$	H.Gly.OH	—	80	271, 344
	Cbzo.Gly.OH	H.Gly.Gly.OH	—	52	271, 244

Note: References 437 to 538 are on pp. 353–355.

* DMF is dimethylformamide.

† With metal catalysts yields up to 80% were obtained.

‡ The product was a cyclo-tetrapeptide.

TABLE XXIV

ANHYDRIDE FORMATION WITH SULFURIC ACID

Acid	Amine	Solvent	Yield, %	References
C₆H₅CO.Gly.OH	H.DL.Ser.OCH₃	DMF*	70	370
Cbzo Gly.OH	H.Gly.OH	DMF	81	370
	H Gly.OC₂H₅	DMF	85	370
	H.L.Ala OH	DMF	87	370
	H.DL.Ala.OH	DMF	75	370
	H.L.Phe.OH	DMF	80	370
	H.DL.Phe.OH	DMF	70	183, 372–375
	H.L.Phe.OC₂H₅	DMF	48	183
Tos Gly.OH	H.L.Phe.OH	DMF	80	5, 370, 375
	H.DL.Phe.OH			370
Cbzo.DL.Ala.OH	H.Gly.OH	—	00	183
Cbzo.L.Ala.OH	H.L.Tyr.OC₂H₅	DMF	87	370
Tos.DL.Ala.OH	H.Gly.OH	DMF	80	183
Cbzo.L.Leu.OH	H.Gly.OH	DMF	64	370
	H.Gly.OC₂H₅	DMF	65	370
Cbzo.DL.Leu OH	H.Gly.OC₂H₅	DMF	87	370
CH₃CO S Bz.L.Cys.OH	H.Gly.OC₂H₅	DMF	73	370
(Cbzo)₂ L-cystine	H.Gly.OC₂H₅	DMF	81	370
Cbzo.L.Phe.OH	H.Gly.OH	DMF	25, 93	183, 370
	H.Gly.OC₂H₅	DMF	83	370
Cbzo.L.Try.OH	H.Ala.OH	DMF	74. 78	370, 375
Cbzo Gly.OH	H.Gly.Gly.OH	DMF	75	375
	H.L.Leu.Gly.OC₂H₅	DMF	78	370
	H.DL.Leu.Gly.OC₂H₅	DMF	>60	370

Note: References 437 to 638 are on pp. 353–356.

* DMF is dimethylformamide.

TABLE XXIV—*Continued*

ANHYDRIDE FORMATION WITH SULFURIC ACID

Acid	Amine	Solvent	Yield, %	References
Tos.Gly.OH	H.DL.Phe.Gly.OH	DMF	92	5, 370, 375
Cbzo.Gly.Gly.OH	H.Gly.OH	DMF	84	370
Cbzo.Gly.L.Phe.OH	H.Gly.OH	DMF	52	183, 372–375
			83	5, 370
			72	183, 372–375
Cbzo.Gly.DL.Phe.OH	H.Gly.OH	DMF	81	370
Cbzo.Gly.L.Phe.OH	H.Gly.OC$_2$H$_5$	DMF	62	370
Cbzo.L.Ala.O–CH$_2$CO.L.Tyr.OH	H.Gly.OC$_2$H$_5$	DMF	36, 78	370, 375
Cbzo.Gly.L.Ala.OH	H.L.Phe.Gly.OH	DMF		
Tos.Gly.L.Phe.OH	OH | H.L.Glu.Gly.NHCH(CH$_2$)$_5$	DMF	71	375
Cbzo.Gly.L.Leu.Gly.OH	H.L.Leu.Gly.OH	—	—	334

Note: References 437 to 538 are on pp. 353–355.

TABLE XXV

ANHYDRIDE FORMATION WITH BENZENESULFONYL CHLORIDE

Acid	Amine	Solvent	Yield, %	Reference
Plth.Gly.OH	H.Gly.OCH$_3$	Pyridine	79	378
	H.DL.Phe.OCH$_3$	Pyridine	86	378
Tos.Gly.OH	H.Gly.OCH$_3$	Pyridine	58	378
Plth.DL.Phe.OH	H.Gly.OCH$_3$	Pyridine	90	378
O,N-(Tos)$_2$.L.Tyr.OH	H.Gly.OCH$_3$	Pyridine	95	378

Note: References 437 to 538 are on pp. 353–355.

TABLE XXVI

ANHYDRIDE FORMATION WITH PIVALYL'S OXYCHLORIDE

Acid	Amine	Solvent	Yield, %	Reference
Cbzo·Gly·OH	H.Gly.OCH₃	THF*	70	130
	H.Gly.OC₂H₅	THF	80	130
	H.Gly.OC₃H₇	THF	05	37
	H.DL.Ala.OCH₂C₆H₅	THF	70	130
	H.DL.Ala.SC₄H₉NO₂-p	THF	53	37
	H.DL.Val.OC₂H₅	THF	74	37
	H.DL.Leu.OC₂H₅	THF	71	130
	H.L.Leu.NHC₆H₅	THF	57	37
	H.DL.Met.OCH₃	THF	05	130
	H.L.Tyr.OC₂H₅	THF	69	130
Cbzo·DL·Ala·OH	H.Gly.OC₂H₅	THF	80	130
	H.Gly.OC₂H₄NO₂-p	THF	70	37
	H.Gly.SC₂H₅	THF	05	37
Cbzo·HO·L·Pro·OH	H.DL.Thr.OCH₃	THF	07	130
Cbzo·DL·Val·OH	H.L.Tyr.OC₂H₅	THF	75 crude	130
Cbzo·DL·Leu·OH	H.L.Tyr.OC₂H₅	THF	88	130
	H.Gly.SC₂H₅	THF	37	37
Cbzo·Gly·OH	H.Gly.OC₂H₅	TUF	90	130
Cbzo·S.Bz.L.Cys.OH	H.Gly.OC₂H₅	TUF	81	130
	H.S.Bz.L.Cys.OC₂H₅	Chloroform	53	454
Cbzo·L·Glu·OH NH₂	H.S.Bz.L.Cys.OC₂H₅	THF	35	454
	H.S.Bz.L.Cys.OC₄H₈C₂H₅	Chloroform	33	454

Note: References 437 to 538 are on pp. 353-355.

* THF is tetrahydrofuran.

TABLE XXVI—*Continued*

ANHYDRIDE FORMATION WITH PHOSPHORUS OXYCHLORIDE

Acid	Amine	Solvent	Yield, %	Reference
Cbzo.Gly.OH	H.DL.Ala.Gly.SC$_6$H$_5$	THF	65	37
Cbzo.S.Bz.L.Cys.OH	H.Gly.DL.Ala.OCH$_2$C$_6$H$_5$	THF	70	130
Cbzo.L.Phe.OH	H.Gly.L.Ala.OC$_2$H$_5$	THF	53–58†	534
	H.Gly.L.Val.OC$_2$H$_5$	THF	50	534
Cbzo.D.Phe.OH	H.Gly.D.Val.OC$_2$H$_5$	THF	50	534
NH$_2$ | Cbzo.L.Glu.OH	H.S.Bz.L.Cys.S.Bz.L.Cys.OC$_2$H$_5$	THF	94	454
Cbzo.DL.Ala.Gly.OH	H.Gly.SC$_6$H$_5$	THF	50	37
Cbzo.Gly.DL.Val.OH	H.DL.Ala.SC$_6$H$_5$	THF	51	37
	H.DL.Leu.SC$_6$H$_5$	THF	63	37
	H.DL.Ileu.SC$_6$H$_5$	THF	33	37
Cbzo.Gly.DL.Leu.OH	H.DL.Val.OCH$_3$	THF	77	130

Note: References 437 to 538 are on pp. 353–355.

† All the optical isomers were prepared.

TABLE XXVII

Anhydride Formation with Distal Carboxyl Groups (Aspartic and Glutamic) — Pb esters

Acid	Amine	Solvent	Yield %	References
Cbzo.Gly.OH	H.Gly.OH	Acetone	71	349, 351
	H.Gly.OC₂H₅	Acetone	71	351
	H.Ala.Ala.OC₂H₅	Acetone	65	351, 352
	H.Leu.OH	Acetone	71	351
	H.L.Tyr.OC₂H₅	Acetone	65	351, 352
Cbzo.Ala.OH	H.Ala.OH	Acetone	76	351, 352
	H.Leu.OC₂H₅	Acetone	63	351, 352
	H.Ala.OC₂H₅	Acetone	63	351, 352
Cbzo.Leu.OH	H.Gly.OC₂H₅	Acetone	55	351
Cbzo.Gly.OH	H.Gly.OH	Acetone	32	351, 352
	H.Gly.Gly.OH	Acetone	7	351, 352

Note: References 437 to 538 are on pp. 353–355.

TABLE XXVIII

ANHYDRIDE FORMATION WITH MISCELLANEOUS PHOSPHATES

Phosphate	Acid	Amine	Solvent	Yield, %	Reference
Silver dibenzyl phosphate	Phth.Gly.OH	H.Gly.OH	Benzene	78	386
	Phth.Gly.OH	H.DL.Phe.OH	Benzene	83 crude	386
Disilver phenyl phosphate	Cbzo.Gly.Cl	H.Gly.OH	Ether	—	22
	Cbzo.Gly.Cl	H.Try.OH	Ether	—	22
	Cbzo.Gly.Cl	H.Gly.Try.OH	Ether	—	22
Diphenyl chlorophosphate	Cbzo.Gly.OH	H.Gly.OH	THF*	10	48
Phenyl dichlorophosphate	Cbzo.Gly.OH	H.Gly.OH	THF	30	48
2',3'-Isopropylideneadenosine-5'-benzylphosphoric acid	Cbzo.Gly.OH	H.Phe.OCH$_3$	—	—	380
	Cbzo.L.Leu.OH	H.Gly.OCH$_3$	Benzene-acetonitrile-dioxane	—	380

Note: References 437 to 538 are on pp. 353–355.

* THF is tetrahydrofuran.

TABLE XXIX

ANHYDRIDES FORMATION WITH PHOSPHITES

Phosphate	Acid	Amine	Solvent	Yield, %	References
Diethyl chlorophosphate	Cbzo.Gly.OH	H.DL.Phe.OC₂H₅	Toluene	62	399, 401, 402, 404, 411
	Cbzo.DL.Ala.OH	H.DL.Phe.OC₂H₅	Toluene	48	399, 401, 402, 404, 411
	(Cbzo).L.Lys.OH	H.Gly.OC₂H₅	Benzene	52	399, 402, 404, 411
Ethylene chlorophosphate	Cbzo.Gly.OH	H.Gly.Gly.OC₂H₅	Benzene	43	399, 401, 402, 404
	Phth.Gly.OH	H.DL.Phe.OC₂H₅	Toluene	71	399, 401, 402, 411
	Cbzo.Gly.OH	H.DL.Phe.OC₂H₅	Diethyl phosphate	81	406
	Cbzo.Gly.OH	H.L.Tyr.OC₂H₅	Diethyl phosphate	79	406
	Cbzo.Gly.L.Phe.OH	H.L.OC₂H₅	Diethyl phosphate	52 L, 14 DL	405
Ethyl dichlorophosphate	Cbzo.Gly.OH	H.DL.Phe.OC₂H₅	Benzene	91	403, 405–408
	Cbzo.Gly.OH	H.L.Tyr.OC₂H₅	Benzene	44	403, 405–408
	Phth.Gly.OH	H.DL.OC₂H₅	Benzene	62	403, 405–408
	Cbzo.DL.Val.OH	H.L.Leu.OC₂H₅	Benzene	81	403, 405–408
	Cbzo.L.Leu.OH	H.Gly.OC₂H₅	Benzene	83	406
	Cbzo.L.Leu.OH	H.Gly.OC₂H₅	Benzene	40	406
	Cbzo.L.Leu.OH	H.OH.OC₂H₅	Benzene	42	406
	Cbzo.L.Phe.OH	H.Gly.OC₂H₅	Benzene	—	403, 405, 407, 408
	Cbzo.DL.Phe.OH	H.Gly.OC₂H₅	Benzene	63	406
	Cbzo.Gly.L.Leu.OH	H.L.Leu.OC₂H₅	Dioxan	64	403, 407, 408
	Cbzo.Gly.L.Leu.OH	H.Gly.OC₂H₅	Benzene	60	406
	Cbzo.Gly.L.Phe.OH	H.L.Leu.OC₂H₅	Benzene	71	408
	Cbzo.Gly.DL.Phe.OH	H.Gly.OC₂H₅	Benzene	406	406
	Cbzo.Gly.DL.Phe.OH	H.Gly.OC₂H₅	Benzene	75–78	403, 405–408

Note: References 437 to 538 are on pp. 353–356.

TABLE XXIX—*Continued*
ANHYDRIDE FORMATION WITH PHOSPHITES

Phosphite	Acid	Amine	Solvent	Yield, %	References
Tetraethyl pyrophosphite	Cbzo.Gly.OH	H.DL.Phe.OC$_2$H$_5$	None	—	407, 408, 535
	Cbzo.L.Tyr.OH	H.Gly.Gly.OC$_2$H$_5$	Diethyl phosphite	—	407, 408, 535

Note: References 487 to 538 are on pp. 353–355.

TABLE XXX
ANHYDRIDE FORMATION WITH DIETHYL CHLOROARSENITE

Acid	Amine	Solvent	Yield, %	References
Cbzo.Gly.OH	H.DL.Phe.OC$_2$H$_5$	Chloroform	52	434, 536, 537
Cbzo.DL.Ala.OH	H.DL.Phe.OC$_2$H$_5$	Toluene	60	434, 536, 537
Cbzo.L.Leu.OH	H.DL.Phe.OC$_2$H$_5$	Toluene	74	434, 536, 537
Cbzo.Gly.OH	H.DL.Phe.OC$_2$H$_5$	Toluene	30	434, 536, 537

Note: References 487 to 538 are on pp. 353–355.

REFERENCES TO TABLES I–XXX

[437] Jatzkewitz, Z. physiol. Chem., Hoppe-Seyler's, **297**, 149 (1954).

[438] Pechmann, Peckham, and Rheiner, J. Am. Chem. Soc., **78**, 238 (1956).

[439] Peckham, Dissertation Abstr., **15**, 1713 (1955).

[440] Cohen and Fry, J. Am. Chem Soc., **79**, 5663 (1956).

[441] Zervas and Katsoyannis, J. Am. Chem. Soc., **77**, 5351 (1955).

[442] Zahn and Kessler, Makromol. Chem., **27**, 219 (1958)

[443] Kollontsch, Gábor, and Hajós, Nature, **177**, 841 (1956)

[444] Kollontsch, Gábor, and Hajós, Chem. Ber., **89**, 2293 (1956)

[445] King, Clark Lewis, and Smyth, J. Chem. Soc., **1954**, 1046.

[446] Vellux, Anatol, and Amard, Bull soc. chim France, **1954**, 1449.

[447] Vellux, Anatol, and Amard, Fr. pat. 1,109,611 [Chem. Zentr. **129**, 5513 (1958)].

[448] Amard and Heymes, Fr. pat. 1,112,766 [Chem Zentr., **129**, 9346 (1958)]

[449] Brit. pat. 787,319 (to UCLAF) [C. A., **52**, 10972b (1958)]

[450] Theodoropoulos, J. Org. Chem., **21**, 1550 (1956).

[451] Pieser, Fieser, Toromanoff, Hirata, Heymann, Tefft, and Bhattacharya, J. Am. Chem. Soc, **78**, 2825 (1956)

[454] Holland and Cohen, J. Am. Chem. Soc, **80**, 3765 (1958).

[455] Birkofer and Hartwig, Chem. Ber., **89**, 1608 (1956).

[456] Maclaren, Savige, and Swan, Australian J Chem., **11**, 345 (1958)

[457] Maclaren, Savige, and Swan, Angew. Chem., **69**, 217 (1956).

[458] Maclaren, Savige, and Swan, Proc. Intern. Wool Textile Conference, Australia, **1955**, C, 164–7, Discussion, p 479 (Pub. 1956).

[459] Wieland, Corda, and Keck, Chem Ber., **87**, 1312 (1954)

[460] Waggana, Winitz, and Fruton, Yale J Biol. and Med, **27**, 11 (1954).

[461] Schlogl, Wessely, and Woelfach, Monatsh., **87**, 425 (1956).

[462] Schwars, Bumpus, and Page, J. Am Chem Soc., **79**, 5697 (1957)

[463] Rittel, Iselin, Kappeler, Riniker, and Schwyzer, Helo Chim. Acta, **40**, 614 (1957)

[466] Schlogl and Fabitschowits, Monatsh **84**, 937 (1953)

[468] Boissonnas, Guttmann, Jaquenoud, and Waller, U.S. pat. 2,852,443 (to Saul and Co.) [C A., **53**, 7042a (1959)].

[469] Merrifield and Woolley, J. Am Chem, Soc, **78**, 4646 (1956).

[461] Merrifield and Woolley, J. Am Chem, Soc, **80**, 6635 (1958)

[462] Bachelard and Trikojus, J. Chem Soc., **1955**, 4641

[467] Theodoropoulos and Craig, J Org Chem., **21**, 1376 (1956).

[468] Berse, Boucher, and Piché, J Org Chem., **22**, 805 (1957).

[469] Hofmann, Johl, Furlenmeier, and Kappeler, J. Am Chem. Soc, **79**, 1636 (1957),

[470] Hofmann and Johl, J Am Chem. Soc, **77**, 2914 (1955).

[471] Guttmann and Boissonnas, Helv. Chim Acta, **41**, 1852 (1958).

[472] Leutsch and Schroder, Monatsh., **88**, 454 (1957).

[473] Hofmann, Med Chem Symposium (Am. Chem Soc), Syracuse, June 17–19, 1958, p. 108.

[474] Batteraby and Robinson, Chem. & Ind (London), **1955**, 42.

[475] Swallow, Lockhart, and Abraham, Biochem J, **70**, 365 (1958),

[476] Kaneko, Shiba, Watarai, Imai, Shimada, and Ueno, Chem & Ind (London), **1957**, 986.

[477] Shiba, Imai, and Kaneko, Bull Chem Soc, Japan, **31**, 244 (1958) [C.A., **52**, 15437d (1958)]

[478] Zervas, Otani, Winitz, and Greenstein, Arch Biochem, Biophys, **75**, 290 (1958)

[477] Weley, Biochem J., **68**, 189 (1958).

[478] Noguchi, Hayakawa, and Nishimura, Nippon Kagaku Zasshi, **77**, 463 (1956) [C A, **52**, 8483b (1958)].

[479] Schlogl and Fabitschowits, Monatsh, **86**, 233 (1955)

[480] Rowlands and Young, Biochem. J., **65**, 518 (1957).

[481] Morozova and Zhenodarova, Zhur. Obshchei Khim., **28**, 1858 (1958) [C.A., **53**, 1316e (1959)]

[482] Holley and Holley, *J. Am. Chem. Soc.*, **74**, 3069 (1952).

[483] Wieland and Ohly, *Ann.*, **605**, 179 (1957).

[484] Hörmann, Grassmann, Wünsch, and Preller, *Chem. Ber.*, **89**, 933 (1956).

[485] Hofmann, Kappeler, Furlenmeier, Woolner, Schwartz, and Thompson, *J. Am. Chem. Soc.*, **79**, 1641 (1957).

[486] Zahn and Kunde, *Angew. Chem.*, **70**, 189 (1958).

[487] Lautsch and Schulz, *Naturwiss.*, **45**, 58 (1958).

[488] Narita, *Biochim. et Biophys. Acta*, **31**, 372 (1959).

[489] Poduška, Rudinger, and Šorm, *Collection Czechoslov. Chem. Communs.*, **20**, 1174 (1955). Published in Czech. in *Chem. Listy.* **49**, 737 (1955) [*C.A.*, **50**, 4016a (1956)].

[490] Herrick and Todd, U.S. pat. 2,723,972 (to du Pont) [*C.A.*, **50**, 4214g (1956)].

[491] Rudinger and Pravda, *Collection Czechoslov. Chem. Communs.*, **23**, 1947 (1958). Published in Czech. in *Chem. Listy*, **57**, 120 (1958) [*C.A.*, **52**, 16233h (1958)].

[492] Van Orden and Smith, *J. Biol. Chem.*, **208**, 751 (1954).

[493] Dunn, *J. Biol. Chem.*, **227**, 575 (1957).

[494] Roeske, Stewart, Stedman, and du Vigneaud, *J. Am. Chem. Soc.*, **78**, 5883 (1956).

[495] Davis and Adams, *Arch. Biochem. Biophys.*, **57**, 301 (1955).

[496] Erlanger, Curran, and Kokowsky, *J. Am. Chem. Soc.*, **80**, 1128 (1958).

[497] King, Clark-Lewis, and Wade, *J. Chem. Soc.*, **1957**, 886.

[498] Davis, *J. Biol. Chem.*, **223**, 935 (1956).

[499] Lutz, Ressler, Nettleton, and du Vigneaud, *J. Am. Chem. Soc.*, **81**, 167 (1959).

[500] Ressler and du Vigneaud, *J. Am. Chem. Soc.*, **79**, 4511 (1957).

[501] Van Orden and Smith, *Federation Proc.*, **13**, 313 (1954).

[502] Herrick and Todd, U.S. pat. 2,723,973 (to du Pont) [*C.A.*, **50**, 4215d (1956)].

[503] Uehio and Izumiya, *Mem. Fac. Sci., Kyushu Univ., Ser. C*, **3**, No. 1, 5 (1958) [*C.A.*, **52**, 14539b (1958)].

[504] Bodanszky and du Vigneaud, *J. Am. Chem. Soc.*, **81**, 1258 (1959).

[505] Bartlett, Jöhl, Roeske, Stedman, Stewart, Ward, and du Vigneaud, *J. Am. Chem. Soc.*, **78**, 2905 (1956).

[506] Kögl, *Gazz. chim. ital.*, **84**, 1223 (1954).

[507] Fr. pat. 1,934,023 (to Boehringer Sohn) [*Chem. Zentr.*, **126**, 6195 (1955)].

[508] Wieland and Sehring, Swiss pat. 315,314 (to Boehringer Sohn) [*Chem. Zentr.*, **128**, 6833 (1957)].

[509] Schramm and Leube, *Makromol. Chem.*, **13**, 117 (1954).

[510] Vaughan, Can. pat. 534,792 (to American Cyanamid) (1956).

[511] Kitaoka, Sakakibara, and Tani, *Bull. Chem. Soc. Japan*, **31**, 802 (1958).

[512] Fr. pat. 1,934,024 (to Boehringer Sohn) [*Chem. Zentr.*, **126**, 11737 (1955)].

[513] Okawa, *Bull. Chem. Soc. Japan*, **30**, 976 (1957).

[514] Ram, Ingle, and Damodavian, *J. Sci. Ind. Research (India)*, **17C**, 21 (1958) [*C.A.*, **52**, 19971a (1958)].

[515] Zahn and Diehl, *Angew. Chem.*, **69**, 135 (1957).

[516] Narita, *Biochim. et Biophys. Acta*, **30**, 352 (1958).

[517] Merrifield, *J. Biol. Chem.*, **232**, 43 (1958).

[518] Katsoyannis and du Vigneaud, *Arch. Biochem. Biophys.*, **78**, 555 (1958).

[519] Amiard, Heymès, and Velluz, *Bull. soc. chim. France*, **1956**, 698.

[520] Mechanic and Levy, *J. Am Chem. Soc.*, **81**, 1889 (1959).

[521] Waisvisz, van der Hoeven, and te Nijenhuis, *J. Am. Chem. Soc.*, **79**, 4524 (1957).

[522] Golubeva, Kil'disheva, and Knuyants, *Doklady Akad. Nauk S.S.S.R.*, **119**, 83 (1958) [*C.A.*, **52**, 14537f (1958)].

[523] Knuyants, Kil'disheva, and Golubera, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk.* **1956**, 1418 [*C.A.*, **51**, 8066d (1957)].

[524] Shabarova, Sokolova, and Prokof'ev, *Zhur. Obshchei Khim.*, **29**, 539 (1959).

[525] Katsoyannis and du Vigneaud, *J. Biol. Chem.*, **233**, 1352 (1958).

[526] Schwyzer, Iselin, Kappeler, Rniker, Rittel, and Zuber, *Helv. Chim. Acta*, **41**, 1287 (1958).

[527] Ressler, *Proc. Soc. Exptl. Biol. Med.*, **92**, 725 (1956)

[518] Hofmann, Woolner, Yajıma, Spühler, Thompson, and Schwartz, *J. Am. Chem. Soc.*, **80**, 6458 (1958).

[519] Schwyzer and Sieber, *Helv. Chim. Acta*, **41**, 1582 (1958).

[520] Fr pat. 1,186,523, Swiss pat 341,168 (1959) to Organon.

[521] Ger pat appl 1,013,656 (to Organon), Derwent, Ger Pat Report, 49, Group 5, p. 3, Aug 15, 1957

[522] Bodansky, Szelke, Tomorkény, and Weisz, *3e Congr intern biochim*, Bruxeiles, Aug. 1–6, 1955, Résumás des communications, p 10

[523] Schallenberg and Calvin, *J. Am. Chem Soc*, **77**, 2779 (1955)

[524] Losse and Schmidt, *Chem Ber*, **91**, 1068 (1958)

[525] Anderson, Young, and Barbaro, Ger pat 945,240 (to American Cyanamid) [*C.A.*, **52**, 11901a (1958)]

[526] Vaughan, U S pat 2,617,796 (to American Cyanamid) [*C A*, **48**, 1435a (1954)]

[527] Vaughan, Canadian pat 534,799 (to American Cyanamid) (1956)

[528] Wieland and Sehring Ger pat 849 243 (to Boehringer Sohn) [*Chem Zentr*, **125**, 5174 (1954)]

CHAPTER 5

DESULFURIZATION WITH RANEY NICKEL*

GEORGE R. PETTIT

University of Maine

EUGENE E. VAN TAMELEN

University of Wisconsin

CONTENTS

INTRODUCTION

The first example of the desulfurization of an organic compound by means of Raney nickel was reported by Bougault in 1940.[1] Since that time the reaction has been used with much success both for synthesis and the determination of structure In general, a Raney nickel desulfurization involves the breaking of a carbon-sulfur bond in an organic substance and, usually, the formation of at least one new carbon-hydrogen bond. The oxidation state of the sulfur does not matter may vary from

$$R{\longrightarrow}SH \xrightarrow{Ni(H)} R{\longrightarrow}H$$

$$R{\longrightarrow}S{\longrightarrow}H' \xrightarrow{Ni(H)} R{\longrightarrow}H + R'{\longrightarrow}H$$
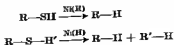
1 Bougault, Cattelain, and Chabrier, Bull soc chim France. [5] 7, 781 (1940)

two to six.   Although the hydrogenolysis of organic compounds containing sulfur has been accomplished by a variety of inorganic reagents, this survey has been restricted to desulfurizations brought about by Raney nickel in which adsorbed hydrogen usually, but not always, has been retained.   The symbol "Ni(H)" will be used to indicate such a reagent.   Desulfurizations effected by nickel-aluminum alloy and aqueous alkali (Schwenk-Papa reduction) also are included.   The analogous Raney nickel deselenization[2, 3] reaction has not been reviewed. Several facets of the Raney nickel desulfurization reaction have recently been reviewed by Challenger.[4]

MECHANISM

Associated with the problem of a hydrogenolytic desulfurization mechanism is the question of hydrogen source.   Bougault[5, 6] in his initial investigations showed that Raney nickel, as ordinarily prepared, contains large quantities of hydrogen that is effective in reducing various organic and inorganic substances.   Others[7] have expressed the belief that it is this "bound" hydrogen that participates in desulfurization reactions. On the other hand, the observation that acetaldehyde was formed in certain thioketal desulfurizations which were carried out in ethanol led to the proposal that it is the hydrogen produced in the dehydrogenation of ethanol to acetaldehyde that is utilized in the desulfurization.[8]   Bonner later demonstrated that the source of hydrogen is actually the nickel and that the production of acetaldehyde from ethanol is simply a concurrent reaction.[9]

In an early paper Bougault suggested as the first step the formation of a nickel mercaptide, which then decomposes to nickel sulfide and a hydrocarbon.[1]   Since then, several groups[10-14] have expressed the belief

$$RSH + Ni \rightarrow RS—Ni—SR + H_2$$
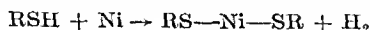
that free radicals are intermediates, and, indeed, such products as one might expect on this basis have been isolated.

[2] Hauptmann and Walter, *J. Am. Chem. Soc.*, **77**, 4029 (1955).

[3] Wiseman and Gould, *J. Am. Chem. Soc.*, **76**, 1706 (1954).

[4] Challenger, *Aspects of the Organic Chemistry of Sulphur*, Butterworths, London, 1959.

[5] Bougault, Cattelain, and Chabrier, *Bull. soc. chim. France*, [5] 5, 1699 (1938).

[6] Bougault, Cattelain, and Chabrier, *Compt. Rend.*, [5] 208, 657, (1939).

[7] Mozingo, Wolf, Harris, and Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

[8] Wolfrom and Karabinos, *J. Am. Chem. Soc.*, **66**, 909 (1944).

[9] Bonner, *J. Am. Chem. Soc.*, **74**, 1033 (1952).

[10] Hauptmann and Wladislaw, *J. Am. Chem. Soc.*, **72**, 707 (1950).

[11] Hauptmann, Walter, and Marino, *J. Am. Chem. Soc.*, **80**, 5832 (1958).

[12] Kenner, Lythgoe, and Todd, *J. Chem. Soc.*, **1948**, 957.

[13] Baker, El-Nawawy, and Ollis, *J. Chem. Soc.*, **1952**, 3163.

[14] Badger and Sasse, *J. Chem. Soc.*, **1957**, 3862.

At present it is believed[13] [14] that the first step in any desulfurization with Raney nickel involves chemisorption of the sulfur atom on the surface of the catalyst. This reaction is followed by fission of the carbon-sulfur bond giving rise to free radicals. The reaction may then proceed by hydrogenation or recombination of the radicals as shown in the accompanying equation. Both reactions have been observed, and the proportion of each is dependent upon the quantity of hydrogen available.

$$R\!H \; + \; R'H$$

$$R\!\!-\!\!S\!\!-\!\!R' \xrightarrow{\text{NiH}} R\cdot \quad \cdot R'$$

$$R\!R \; + \; R\!R' \; + \; R'R'$$
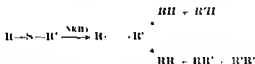
Deactivated catalysts afford greater yields of the dimeric products, while massive amounts of active Raney nickel favor hydrogenation. Desulfurization of 2-benzoylthiophene (I),[16] diphenyl disulfide (II),[11] and 2-naphthyl thiobenzoate (III)[11] may be cited as examples

$$\underset{\text{I}}{\overset{}{\boxed{}\!\text{COC}_6\text{H}_5}} \xrightarrow[\text{47 60\%}]{\text{NiH(R.7)}} \text{C}_4\text{H}_9\text{CO(CH}_2\text{)}_5\text{CH}_3 + \text{C}_4\text{H}_9\text{CO(CH}_2\text{)}_5\text{COC}_6\text{H}_5 \quad 1\ 8\%$$

$$\underset{\text{II}}{(\text{C}_6\text{H}_5\text{S})_2} \xrightarrow[\text{(degassed at 200°)}]{\text{NiH, 200°}} (\text{C}_6\text{H}_5)_2 + \text{C}_6\text{H}_6 + p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4\text{C}_6\text{H}_5$$

$$64\% \qquad 18\% \qquad 0 18\%$$

$$\underset{\text{III}}{2\cdot\text{C}_{10}\text{H}_7\text{SCOC}_6\text{H}_5} \xrightarrow[\text{(degassed at 200°)}]{\text{NiH}} 2,2'\text{-}(\text{C}_{10}\text{H}_7)_2 + 2\cdot\text{C}_{10}\text{H}_7\text{C}_6\text{H}_5$$

$$50\% \qquad 18\%$$

$$+ \text{C}_{12}\text{H}_{10} + (\text{C}_6\text{H}_5)_2$$

$$\text{trace} \qquad \text{trace}$$
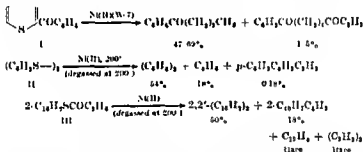
The disulfide II, on treatment at 140° with Raney nickel degassed at 200°, is converted to diphenyl sulfide in 87% yield.[11] Apparently at 140° the carbon-sulfur bonds remain intact for the most part, whereas in the vicinity of 200° they are cleaved to form phenyl radicals. The isolation of benzene indicates that even the small quantity of hydrogen remaining on the nickel after degassing at 200° is still available for hydrogenation. Utilization of Raney nickel degassed at 500° and containing 0.5 ml of hydrogen per gram demonstrated[13] that the yield of biaryl was never less, and in some cases was more, than that observed when the catalyst degassed at 200° was used.

Because different products are obtained when nickel catalysts containing varying amounts of adsorbed hydrogen are employed, it has been suggested that this hydrogen actually causes the fission of the carbon-sulfur bond.[11]

The loss of carbon monoxide during the desulfurization of thioesters with degassed Raney nickel as illustrated with the ester III above has been confirmed.[15]

The stereochemical course of desulfurization has been studied by Bonner.[16,17] The amides of both dextro- and levo-rotatory 2-phenyl-2-(phenylmercapto)propionic acid afforded completely racemized 2-phenylpropionamide, as did both optically pure forms of the corresponding sulfoxides. These results point to a radical mechanism. However, the sulfones corresponding to the same phenylmercaptoamides were converted with nearly complete retention of optical activity to the desulfurized products. Although the configurational relationships of the starting and desulfurized materials were not known, the rotational data suggest that desulfurization occurred with inversion. Bonner suggested initial adsorption of the sulfone on the nickel surface through the oxygen of the sulfone function, followed by interaction with an adjacent hydrogen atom in such a way as to break a carbon-sulfur bond and, simultaneously, to form an optically active reduction product.[17a]

The way in which the Schwenk-Papa method differs mechanistically (if at all) from desulfurization with prepared nickel catalysts is not known.

SCOPE AND LIMITATIONS

A number of the side reactions that occur during desulfurizations with Raney nickel were foreshadowed by the early investigation of Mozingo, Spencer, and Folkers[18] who subjected various reducible substances to representative conditions of the desulfurization reaction. Olefins were found to become saturated, and aliphatic ketones were converted to the corresponding alcohols. Both azoxybenzene and hydrazobenzene suffered reductive cleavage of the nitrogen-nitrogen bond and, in ethanol as the solvent, yielded N-ethylaniline. The latter type of reaction subsequently was shown to be a general procedure for effecting N-alkylation.[19-21] Base-catalyzed C-alkylations with alcohols also have been observed to occur in the presence of Raney nickel.[22,23,23a] All these reactions have

[15] Hauptmann and Wladislaw, *J. Am. Chem. Soc.*, **72**, 710 (1950).

[16] Bonner, *J. Am. Chem. Soc.*, **74**, 1034 (1952).

[17] Bonner, *J. Am. Chem. Soc.*, **74**, 5089 (1952).

[17a] Cf. refs. 307 and 342 for more recent studies pertinent to this subject.

[18] Mozingo, Spencer, and Folkers, *J. Am. Chem. Soc.*, **66**, 1859 (1944).

[19] Kao, Tilak, and Venkataraman, *J. Sci. Ind. Research (India)*, **14B**, 624 (1955) [*C.A.*, **50**, 13771 (1956)].

[20] Venkataraman, *J. Indian Chem. Soc.*, **35**, 1 (1958).

[21] Rice, Kohn, and Daasch, *J. Org. Chem.*, **23**, 1352 (1958).

[22] Wenkert and Bringi, *J. Amer. Chem. Soc.*, **80**, 5575 (1958).

[23] Becker, *J. Chem. Educ.*, **36**, 119 (1959).

[23a] Densa, *Experientia*, **15**, 95 (1959).

since been observed to occur during desulfurization.[12, 14, 20, 24-35] The work of Mozingo and collaborators, in addition, implied hydrogenolytic removal of oxygen from the benzylic position;[26, 37] aliphatic carboxyl and ester groups, however, appeared to be stable under desulfurization conditions. An exception to the latter generalization involves hydrogenolysis of ketol acetates.[32a]

Additional examples[38-43] indicate that complete hydrogenolysis, rather than selective desulfurization, of a carbon bound to both sulfur and nitrogen can take place. Furthermore, compounds having carbon singly bound to both sulfur and oxygen (hemithioacetal or hemithioketal) can regenerate the parent carbonyl compound.[44-46]

Aromatic compounds containing nitrogen in various oxidized states have been reduced to primary amines concurrently with desulfurization; examples include nitro,[47] hydroxylamino,[44, 48] and nitroso[50] functions.

Several examples involving saturation of an aromatic nucleus have been

[14] Stork, van Tamelen, Friedman, and Burgstahler, *J Am Chem Soc*, 75, 384 (1953).

[15] Ballard Melstrom, and Smith, in *The Chemistry of Penicillin*, p 956, Princeton Univ. Press, 1949

[20] Cronyn *J Org Chem*, 14, 1013 (1949)

[24] Kornfeld, *J Org Chem*, 16, 131 (1951)

[25] Knowles and Thompson, *J Am Chem Soc*, 79, 3212 (1957)

[26] Ernest, *Collection Czechoslov Chem Communs*, 21, 1169 (1956) [*C A*, 50, 13749 (1956)].

[27] Hnĕvová, Šmolý, and Ernest, *Collection Czechoslov Chem Commun*, 21, 1459 (1956) [*C A*, 50, 13749 (1956)]

[32a] Walborsky, *J Org Chem*, 18, 702 (1953)

[35] Wilds, Zeitschel, Sutton, and Johnson, *J Org Chem*, 19, 255 (1954)

[37] Bun Höd and Sy, *J Org Chem*, 23, 97 (1958)

[38] Gol'dfarb and Konstantinov, *Izvest Akad Nauk S.S.S R*, Otdel. Khim. Nauk, 1956, 992 [*C A*, 51, 5041 (1957)]

[39] Lüttringhaus and Deckert, *Angew Chem*, 67, 275 (1955)

[40] Gut, Prins, and Heckman, *Helv Chim Acta*, 30, 743 (1947).

[41] Hussey, Liao, and Baker, *J Am Chem Soc*, 75, 4727 (1953).

[42] Cf refs 390, 391, and 417

[43] Baddiley, *J Chem Soc*, 1950, 3693

[44] Kaczka, Folkers, Mozingo, and Folkers, in *The Chemistry of Penicillin*, pp 546, 250, Princeton Univ. Press, 1949

[45] McLamore, Celmer, Bogert, Pennington, Sobin, and Solomons, *J Am Chem. Soc*, 75, 105 (1953)

[46] Badger and Kowanko, *J Chem Soc*, 1957, 1652.

[47] Rylander and Campagne, *J Org Chem*, 15, 249 (1950)

[48] Hurd and Rudner, *J Am Chem Soc*, 73, 5157 (1951).

[49] Jaeger and Smith, *J Chem Soc*, 1955, 160

[50] Djerassi, Gorman, and Henry, *J Am Chem Soc*, 77, 4647 (1955).

[51] Djerassi, Shamma, and Kan, *J. Am Chem Soc*, 80, 4723 (1958)

[52] Djerassi, Gorman, and Henry, *Helv. Chim. Acta*, 31, 65 (1948)

[53] Elderfield and Claflin, *J Am Chem Soc*, 74, 2953 (1952)

[54] Gol'dfarb, Fabrichnyĭ, and Shalavina, *Izvest Akad Nauk S S.S.R.*, Otdel. Khim Nauk, 1956, 1276 [*C.A.*, 51, 5702 (1957)].

[55] Cavalier, Tinkar, and Bendich, *J Am Chem Soc*, 71, 533 (1949).

reported,[51-54] although aromatic rings originally were reported to remain unchanged during nickel desulfurization.[36]

An early prediction by Schröter[55] concerning the possibility of using Raney nickel desulfurization for the quantitative determination of sulfur in carbon compounds has been realized.   The nickel sulfide resulting from desulfurization is treated with acid, and the liberated hydrogen sulfide is determined by titration with mercuric acetate[56] or by a polarographic method.[57]   The quantitative studies point out that approximately 95% of the original sulfur is converted to nickel sulfide during desulfurization. The fate of any remaining sulfur has not been established.[56]

Many of the side reactions involving reduction described above can be used to advantage or circumvented by the use of *deactivated*, rather than *active*, Raney nickel.   Several apparent discrepancies arise in the consideration of occurrence or absence of reduction accompanying desulfurization;   these can be explained by assuming differences in reaction conditions or by differences in nickel reagents, which may vary in activity with age or method of preparation.   In general, the Raney nickel reagent used for desulfurization may lead to side reactions involving reduction, oxidation, rearrangement, or condensation.[58]

Thiols

Aliphatic and aromatic mercaptans ordinarily can be desulfurized by treatment with Raney nickel, the product usually being the one resulting from cleavage of the carbon-sulfur bond and the formation of a new carbon-hydrogen bond.   Such desulfurizations range from relatively simple examples like the formation of ethane from 1,2-ethanedithiol[1] or naphthalene from naphthalene-β-thiol[9] to the more complex case involving the transformation of 2-mercaptobenzothiazole (IV) to the mixture of products shown. The reaction is carried out in boiling methanolic sodium hydroxide solution.[11]

The desulfurization of mercaptans (as well as other organic sulfur

[51] G. R. Pettit and R. E. Kadunce, unpublished experiments

[52] Compare ref. 99.

[53] Davies and Porter, J. Chem Soc., 1957, 459.

[54] Desai, Kamanathan, and Venkataraman, J. Sci. Ind. Research. (India), 15B, 279 (1956) [C.A., 51, 3596 (1957)]

[55] Schröter, in Newer Methods of Preparative Organic Chemistry, p. 74, Interscience, New York, 1918.

[56] Granatelli, Anal. Chem., 31, 151 (1959).

[57] Trifonov, Ivanov, and Pavlov, Compt. rend. acad. bulgare sci., 7, 1 (1954) [C.A., 49, 6775 (1955)].

[58] Lieber and Morritz, in Advances in Catalysis, Vol. V, p. 417, Academic Press, New York 1953.
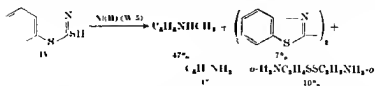
compounds is characterized by a high order of selectivity; only occasion-

ally do side reactions interfere and rarely does an alternate reaction supervene A striking example is the desulfurization of 3-mercapto-tetrathiophene [18] in which the mercapto group was removed without attack on the thioether linkage On the other hand, N-(β-mercaptoethyl)-2-benzoylisobutyramide suffered marked reduction of the keto carbonyl group on desulfurization [18] Thiol derivatives of carbohydrates can be hydro-genolyzed without complication for example, 1,6-dithiodulcitol (V) was converted, after acetylation, to the tetraacetyl derivative of 1,6-dideoxydulcitol (VI) [40]
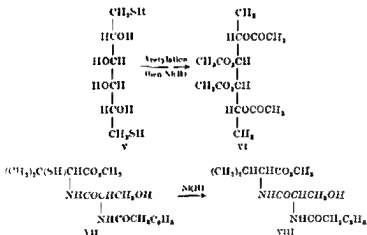
Desulfurization of thiols has been employed extensively for deter-mination of structure, particularly in the penicillin series For example, N-(N-phenylacetyl-L-seryl)-d-penicillamine methyl ester (VII) gave the corresponding D-valine methyl ester VIII,[41] and benzylpenicillamine (IX) led to dethiobenzylpenicillamine (X).[42] β,β'-Dimercaptoisobutyric acid,

[18] Miles and Owen, J Chem. Soc , 1952, 817.
[40] Bladon, Overend, Owen, and Wiggins, J Chem Soc , 1950, 3000
[41] Baker and Ollis, J Chem. Soc , 1951, 556
[42] Cook, in The Chemistry of Penicillin, p 118, Princeton Univ. Press, 1949

reported,[51-54] although aromatic rings originally were reported to remain unchanged during nickel desulfurization.[36]

An early prediction by Schröter[55] concerning the possibility of using Raney nickel desulfurization for the quantitative determination of sulfur in carbon compounds has been realized. The nickel sulfide resulting from desulfurization is treated with acid, and the liberated hydrogen sulfide is determined by titration with mercuric acetate[56] or by a polarographic method.[57] The quantitative studies point out that approximately 95% of the original sulfur is converted to nickel sulfide during desulfurization. The fate of any remaining sulfur has not been established.[56]

Many of the side reactions involving reduction described above can be used to advantage or circumvented by the use of *deactivated*, rather than *active*, Raney nickel. Several apparent discrepancies arise in the consideration of occurrence or absence of reduction accompanying desulfurization; these can be explained by assuming differences in reaction conditions or by differences in nickel reagents, which may vary in activity with age or method of preparation. In general, the Raney nickel reagent used for desulfurization may lead to side reactions involving reduction, oxidation, rearrangement, or condensation.[58]

Thiols

Aliphatic and aromatic mercaptans ordinarily can be desulfurized by treatment with Raney nickel, the product usually being the one resulting from cleavage of the carbon-sulfur bond and the formation of a new carbon-hydrogen bond. Such desulfurizations range from relatively simple examples like the formation of ethane from 1,2-ethanedithiol[1] or naphthalene from naphthalene-β-thiol[9] to the more complex case involving the transformation of 2-mercaptobenzothiazole (IV) to the mixture of products shown. The reaction is carried out in boiling methanolic sodium hydroxide solution.[41]

The desulfurization of mercaptans (as well as other organic sulfur

[51] G. R. Petti and R. E. Kadunce, unpublished experiments

[52] Compare ref 99

[53] Davies and Porter J. Chem Soc., 1957, 459.

[54] Desai, Ramanathan, and Venkataraman, J. Sci. Ind. Research. (India), 15B, 279 (1956) [C.A., 51, 3596 (1957)]

[55] Schröter, in Newer Methods of Preparative Organic Chemistry, p. 74, Interscience, New York, 1948.

[56] Granatelli, Anal. Chem., 31, 434 (1959).

[57] Trifonov, Ivanov, and Pavlov, Compt. rend. acad. bulgare sci. 7, 1 (1954, 'C.A., 49, 6775 (1955)).

[58] Lieber and Morritz, in Advances in Catalysis, Vol. V, p. 417, Academic Press, New York, 1953.

compounds is characterized by a high order of selectivity; only occasion-
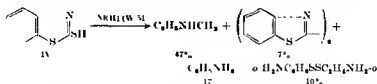
-ally do side reactions interfere, and rarely does an alternate reaction supervene. A striking example is the desulfurization of 3-mercapto-tetrahydrothiophene,[19] in which the mercapto group was removed without attack on the thioether linkage. On the other hand, N-(β-mercaptoethyl)-2-benzoylisobutyramide suffered reduction of the keto group on desulfurization.[33] Thiol derivatives of carbohydrates can be hydrogenolyzed without complication. for example, 1,6-dithiodulcitol (V) was converted, after acetylation, to the tetraacetyl derivative of 1,6-dideoxydulcitol (VI).[60]

$$\begin{array}{ccc}
CH_2SH & & CH_3 \\
| & & | \\
HCOH & & HCOCOCH_3 \\
| & & | \\
HOCH & \xrightarrow[\text{Ren NiH}]{\text{Acetylation}} & CH_3CO_2CH \\
| & & | \\
HOCH & & CH_3CO_2CH \\
| & & | \\
HCOH & & HCOCOCH_3 \\
| & & | \\
CH_2SH & & CH_3 \\
V & & VI
\end{array}$$

$$\begin{array}{ccc}
(CH_3)_2CHCH_2CHCO_2CH_3 & & (CH_3)_2CHCH_2CHCO_2CH_3 \\
| & \xrightarrow{\text{NiH}} & | \\
NHCOCHCH_2OH & & NHCOCHCH_2OH \\
| & & | \\
NHCOCH_2C_6H_5 & & NHCOCH_2C_6H_5 \\
VII & & IX
\end{array}$$
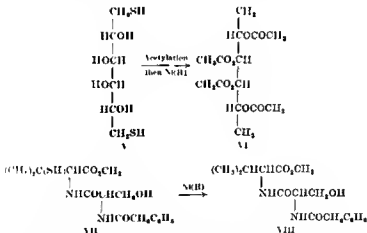
Desulfurization of thiols has been employed extensively for determination of structure, particularly in the penicillin series. For example, N-(N-phenylacetyl-L-seryl)-d-penicillamine methyl ester (VII) gave the corresponding D-valine methyl ester VIII,[61] and benzylpenicillamine (IX) led to dethiobenzylpenicillamine (X).[62] β,β'-Dimercaptoisobutyric acid,

[69] Miles and Owen, J Chem. Soc., 1952, 817.
[61] Bladon, Overend, Owen, and Wiggins, J Chem Soc, 1959, 3000
[62] Baker and Ollis, J. Chem. Soc., 1951, 358
[63] Cook, in The Chemistry of Penicillin, p 116, Princeton Univ Press, 1949

$$\text{NCH(CO}_2\text{H)C(SH)(CH}_3)_2 \xrightarrow{\text{Ni(H)}} \text{NCH(CO}_2\text{H)CH(CH}_3)_2$$

$$\text{CH}_2\text{C}_6\text{H}_5 \qquad\qquad\qquad \text{CH}_2\text{C}_6\text{H}_5$$

IX   X
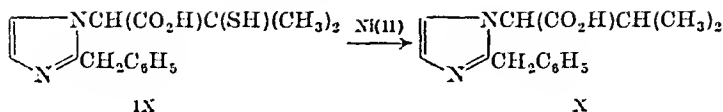
the reduction product of a disulfide isolated from asparagus, was identified in part by desulfurization, which afforded isobutyric acid.[63]

The literature is rich in examples of desulfurization of heterocyclic bases with one or more thiol groups attached directly to the aromatic ring. Such reactions have been used for the synthesis of otherwise difficultly obtainable substances. Thus imidazoles can be prepared by removal of sulfur from thiohydantoins, e.g., XI → XII, which may be considered to react in the tautomeric 2,4-mercaptoimidazole form; imidazole itself was obtained in 25% yield by this method.[64] In a similar fashion, mercapto-

XI   XII
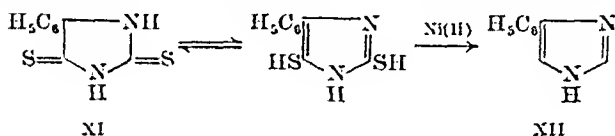
pyrimidines serve as useful precursors for pyrimidines; the parent heterocycle was formed in 17% yield when the reaction was carried out in water at $50°$.[65] Hydroxyl and amino substituents do not interfere; for example, 2-mercapto-5,6-diamino-4-hydroxypyrimidine (XIII) was

XIII   XIV
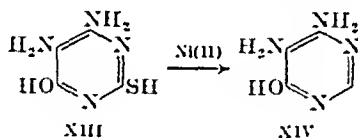
transformed into the expected product XIV in 89% yield.[66] Selective removal of sulfur in the presence of a halogen substituent may be exemplified by the desulfurization of 4-mercapto-5-amino-6-chloropyrimidine (XV) in 25% aqueous ammonia.[67]

Triazoles and triazines are obtainable by parallel reactions; desulfuri-

XV
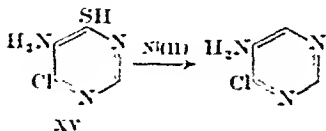
zations of 3-phenyl-5-mercapto-1,2,4-triazine (XVI)[68] and 2-amino-4-mercapto-6-benzyl-1,3,5-triazine (XVII)[69] serve as illustrations.
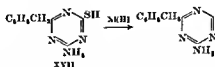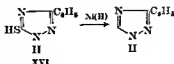
Although a small amount of thiazole is formed on desulfurization of a 2-mercaptothiazole, the preponderant product usually is a completely desulfurized material For example, acetophenone was obtained from 4-phenyl-2-mercaptothiazole (XVIII)[42] and aniline from 2-mercaptobenzothiazole (IV).[42] With a partially degassed W-7 Raney nickel
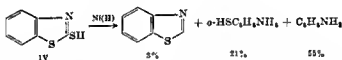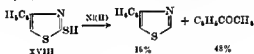
catalyst[70] in methanol, desulfurization of the thiol IV follows a somewhat different course.[41]
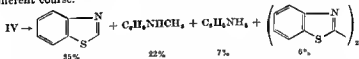
Desulfurization of 6-mercaptopurine (XIX) in ethanolic ammonium hydroxide solution or in boiling water affords purine[71] A number of
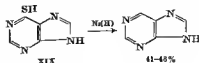
[68] Hoggarth, *J Chem Soc*, **1949**, 1160
[69] Russell, Hitchings, Chase, and Walker, *J Am Chem Soc*, **74**, 5403 (1952).
[70] Badger, Rodda, and Sasse, *J Chem Soc*, **1953**, 4777
[71] Beaman, *J Am Chem Soc*, **76**, 5633 (1954)

pyrimidines related to XX were easily converted to sulfur-free products in yields of 44–84%.[71a] Attempted desulfurizations of pteridinethiol[72] and several purinethiols[73] have been reported to be unsuccessful.
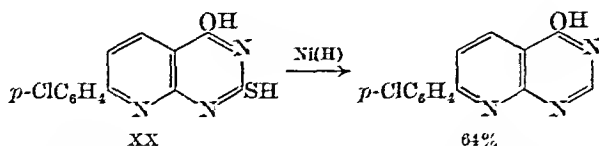
Raney nickel desulfurization of 2β-mercaptocholestan-3β-ol (XXI) in acetone affords predominantly cholestan-3β-ol accompanied by cholestan-3-one (XXII). In benzene as solvent. the thiol XXI is converted to the
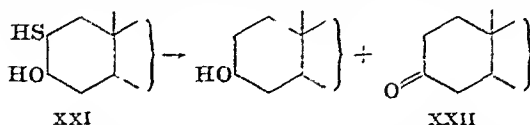
ketone XXII in 80% yield.[45]   Comparable hydrogen transfers have been observed, under similar conditions, in reactions not involving desulfurization.[45, 74]

Thioethers

Desulfurization of thioethers can be carried out selectively in the presence of other reducible groups.   Dibenzyl sulfide, 4-methylmercaptobutyric acid, and diphenyl sulfide are a few of the many sulfides which have been hydrogenolyzed in good yield to the expected products: toluene, butyric acid, and benzene, respectively.[7]

Ketones possessing a thioether function have been desulfurized successfully without reduction of the carbonyl group.   For example, α-thioethyldeoxybenzoin yielded deoxybenzoin[75] on treatment with Raney nickel partially deactivated by contact with acetone.

Intramolecular cyclization has been reported to occur during the desulfurization of certain cyclic thioethers.[76]   Noteworthy is the production of bicyclo[2.2.1]heptane (XXIV) from the sulfide XXIII.   The product of internal cyclization is usually obtained in poor yield.   However, it is conceivable that the proportion might be increased by employing hydrogen-poor Raney nickel.   For example. nickel from which hydrogen
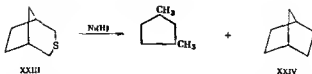
has been wholly or partly removed by heating[4, 10, 11, 15, 17, 75] often produces desulfurization without hydrogenolysis, e.g., the removal of sulfur from di-(p-methoxyphenyl) sulfide forming p,p'-dimethoxybiphenyl[75]

There are several examples of thioether desulfurization accompanied by additional hydrogenation. One is the selective reduction of the acetonide XXV in acetone solution[76] Hydrogenolysis of the benzyl ether
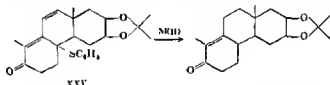
XXVI concomitant with desulfurization was accomplished in 63%
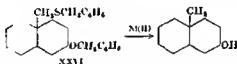
yield[77] A similar reaction took place when trans-2-phenylmercapto-1-indanol was subjected to Raney nickel desulfurization in refluxing
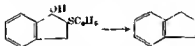
ethanol.[78] Reduction of a cyclopropane ring occurred in good yield during desulfurization of 2,3-dihydrothianaphthen 2 3-ylene acetic acid (XXVII) with W-7 Raney nickel[79]
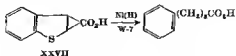
[77] Hauptmann, J Am Chem Soc, 69, 562 (1947)
[78] Hauptmann, Wladislaw, Nazario, and Walter, Ann, 576, 45 (1952)
[79] Ford, Pitkethly, and Young Tetrahedron, 4, 325 (1958)

Other examples include the hydrogenation at room temperature of 1-methyl-6-methylthio-3,4-dihydro-2-pyridone (XXVIII)[80] and partial reduction of the indoline XXIX.[81]

XXVIII

XXIX
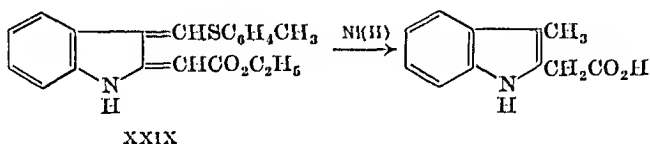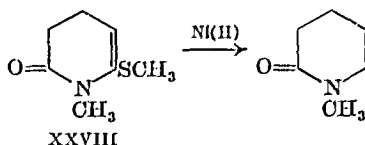
Two of the few unsuccessful attempts at desulfurization of thioethers involve the heterocyclic compounds XXX and XXXI; sulfur could not be abstracted from either molecule.[82] Failure to effect desulfurization of the purine XXXI was attributed to bond formation between the acidic

XXX
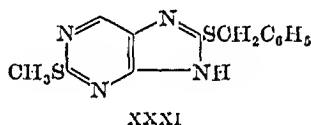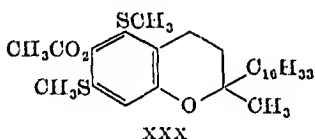
XXXI

—NH group and nickel.[83] However, ethylmercaptodihydrothebainone (XXXII), a thioether of some complexity, was smoothly converted to dihydrothebainone.[84]

XXXII
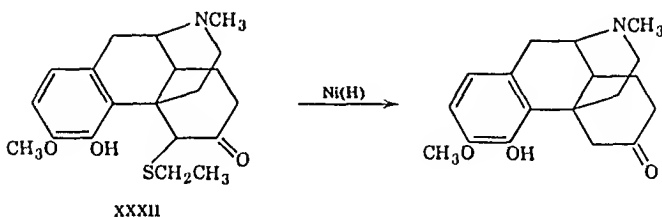
[80] Renault, Ann. chim. (Paris), 10, 135 (1955) [C.A., 50, 9408 (1956)].
[81] Behringer and Weissauer, Chem. Ber., 85, 743 (1952).
[82] Karrer and Dutta, Helv. Chim. Acta, 31, 2080 (1948).
[83] Baker, Joseph, and Schaub, J. Org. Chem., 19, 631 (1954).
[84] Perrine and Small, J. Org. Chem., 17, 1540 (1952).

Various amino acids have been correlated stereochemically by the replacement of sulfur by hydrogen. (+)-Methionine, for example, afforded (−)-α-aminobutyric acid by a route that cannot involve inversion at the asymmetric center [63]

As a purely synthetic tool, the desulfurization reaction was used to advantage in the total synthesis of cantharidin (XXXIII).[64] The tricyclic diol XXXIV was transformed into an intermediate (XXXV) possessing the desired angular methyl groups, after which stepwise oxidative degradation gave cantharidin.
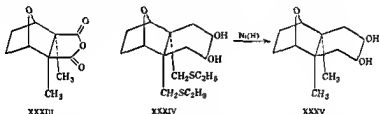
Removal of the thioglycolic acid side chain from the naphthoquinone XXXVI constituted a synthesis of plumbagin (XXXVII). Accompanying the latter in small amount was the product XXXVIII resulting from isomerization and further reduction [66,67] Several deoxy pentose and
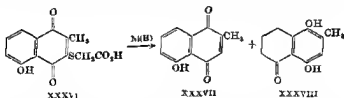
hexose derivatives have been obtained by desulfurization of the appropriate thioether. The dimethylacetal of 2-ethylthioglucose (XXXIX) yielded XL,[68] and 3-methylthio-β-methyl-1-xylopyranoside (XLI) formed 3-deoxy-β-methyl-1-xylopyranoside (XLII).[69]

One finds in the thioether series, as in the thiol series, a number of transformations involving pyrimidines, among which may be cited the

[63] Vogler, *Helv Chim Acta*, **30**, 1766 (1947)
[64] Thomson, *J Chem Soc*, **1951**, 1237
[65] Thomson, *J Chem Soc*, **1952**, 1822.
[66] Bolliger and Schmid, *Helv Chim Acta*, **34**, 1997 (1951)
[67] Mukherjee and Todd, *J. Chem Soc*, **1947**, 969

$$
\begin{array}{ccc}
\text{CH(OCH}_3)_2 & & \text{CH(OCH}_3)_2 \\
| & & | \\
\text{HCSC}_2\text{H}_5 & & \text{CH}_2 \\
| & & | \\
\text{HOCH} & \xrightarrow{\text{Ni(H)}} & \text{HOCH} \\
| & & | \\
\text{HCOH} & & \text{HCOH} \\
| & & | \\
\text{HCOH} & & \text{HCOH} \\
| & & | \\
\text{CH}_2\text{OH} & & \text{CH}_2\text{OH} \\
\text{XXXIX} & & \text{XL}
\end{array}
$$

XLI $\xrightarrow{\text{Ni(H)}}$ XLII
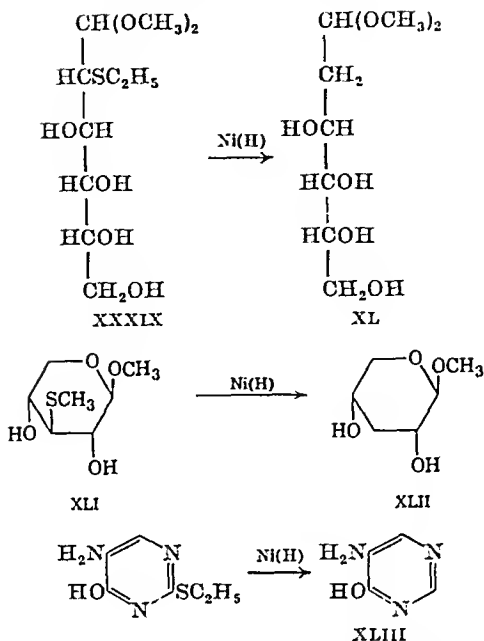
XLIII

preparation of 4-hydroxy-5-aminopyrimidine (XLIII).[90] In the purine group, adenine (XLV) was prepared from the 2-methylmercapto derivative XLIV;[91] a new synthesis of adenosine (XLVII) was realized by the

XLIV $\xrightarrow{\text{Ni(H)}}$ XLV
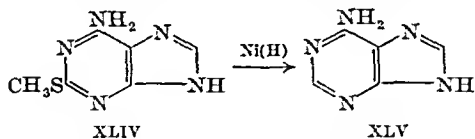
desulfurization of a 2-methylmercapto precursor[92] or its acetyl derivative, XLVI (R = H or CH_3CO).[93]

XLVI $\xrightarrow{\text{Ni(H)}}$ XLVII
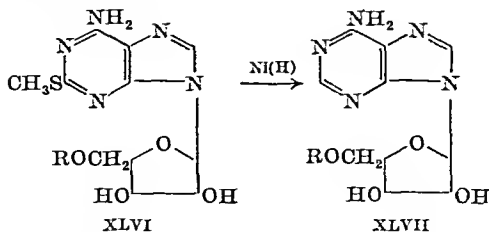
[90] Boarland and McOmie, *J. Chem. Soc.*, 1952, 4942.
[91] Bendich, Tinker, and Brown, *J. Am. Chem. Soc.*, 70, 3109 (1948).
[92] Davoll and Lowy, *J. Am. Chem. Soc.*, 74, 1563 (1952).
[93] Kenner, Taylor, and Todd, *J. Chem. Soc.*, 1949, 1620.

Desulfurization has been employed in a number of important structural studies. One of the most revealing techniques of degradation applied in the study of biotin was desulfurization, which converted biotin methyl ester (XLVIII) to dethiobiotin methyl ester (XLIX).[94] Because one of
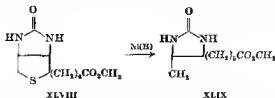
the asymmetric centers is destroyed in the process of sulfur removal, the reaction also proved of value in the stereochemical correlation of various synthetic biotin isomers with the natural product[95] Most carefully scrutinized in the penicillin series was benzylpenicillin (L),[39,59] which, as the sodium salt, yielded three products, mainly dethiobenzylpenicillin (LI), along with phenylacetyl-L-alanyl-D-valine (LII) and the isobutyl-amide of phenylacetyl-L-alanine (LIII). The valine derivative arises by
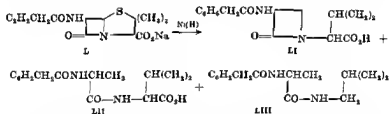
complete hydrogenolysis of the carbon atom bearing both nitrogen and sulfur, a phenomenon which is not unique, the formation of LIII, on the other hand, is a curious result which may involve a decarboxylation-β-elimination followed by reduction Hydrogenolysis of the type leading to LII was later encountered in investigation of the antibiotic actithiazone acetamide, along with the anticipated methyl 7-acetamidoheptanoate, was obtained on desulfurization of the methyl ester LIV of the natural

[94] Du Vigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy, and Harris, *J. Biol. Chem.*, 146, 475 (1942)

[95] Harris, Mozingo, Wolf, Wilson, and Folkers, *J. Am. Chem. Soc.*, 67, 2102 (1945)

[96] Adkins, Brutschy, and McWhirter, *J. Am. Chem. Soc.*, 70, 2619 (1948)

product.[40] Interestingly enough, a compound of similar constitution, LV, has been reported to form the amide LVI as a result of carbon-sulfur cleavage only.[97]

LV → LVI
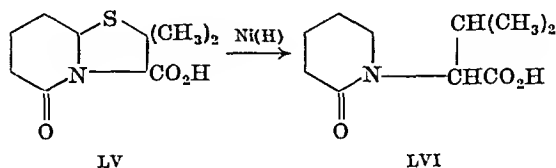
Thiadamantane, an unusual constituent of Middle East crude oil, was assigned the structure LVII, mainly on the basis of its desulfurization to bicyclo[3.3.1]nonane.[98]
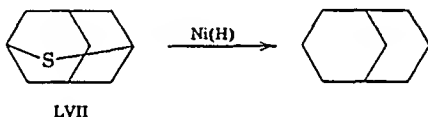
LVII

Desulfurization studies also have contributed to the knowledge of thioindigo dye chemistry.[99] Hydrogenolysis of Durindone Brown GS (LVIII) with Raney nickel alloy in aqueous sodium hydroxide gave 1,2-di-(α-naphthoyl)ethane (LIX) and a yellow liquid of unknown structure. Under essentially the same condition, Ciba Brown 2R afforded similar

LVIII → LIX
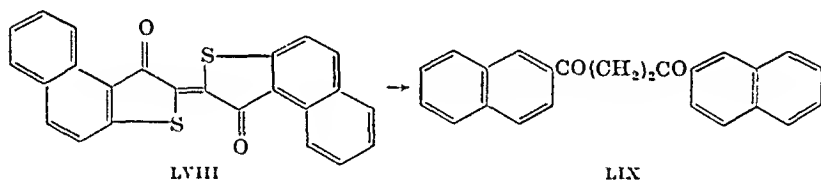
products. In conjunction with other evidence, it was concluded that Ciba Brown 2R is probably identical with Durindone Brown GS.[19]

Striking examples of selective hydrogenolytic removal of sulfur appear in the steroid field. Among these are the conversions of the benzyl thio enol ethers of cholestenone (LX) and progesterone (LXI) to 3,5-cholestadiene (LXII)[100] and 3,5-pregnadien-20-one (LXIII),[101] respectively.

$C_6H_5CH_2S$ LX $\xrightarrow{\text{Ni(H)}}$ LXII

COCH$_3$

$C_6H_5CH_2S$ LXI $\xrightarrow{\text{Ni(H)}}$ LXIII
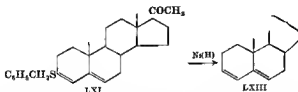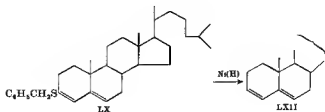
Attack at the double bonds was prevented by the use of acetone-deactivated nickel

It is noteworthy that desulfurization of the steroidal sapogenin LXIV in acetone led to a mixture of 22β-spirosta-3,5,7-triene and the partially reduced 22β-spirosta-5,7-diene (LXV).[102] Both the double bond and the

$HOCH_2CH_2S$ LXIV $\xrightarrow{\text{Ni(H)}}$ LXV
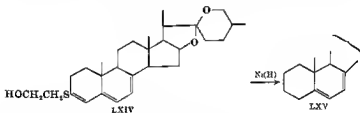
carbonyl group of 3-ethylthio-5-cholesten-7-one are reduced during desulfurization with ordinary nickel [103]

Disulfides

Desulfurization of disulfides proceeds as expected, the removal of both sulfur atoms being accompanied by the introduction of two hydrogen For

$$R—S—S—R' \xrightarrow{\text{Ni(H)}} R—H + R'—H$$

example, L-cystine (LXVI) and its di-N-benzoyl derivative[7] yielded L-alanine.[104]

[102] Djerassi and Gorman, *J Am Chem Soc*, **75**, 3704 (1953)
[103] Ralls, Dodson, and Riegel, *J Am Chem Soc*, **71**, 3320 (1949)
[104] Fonken and Mozingo, *J Am Chem Soc*, **69**, 1212 (1947)

$$SCH_2CH(NH_2)CO_2H$$
$$| \qquad\qquad \xrightarrow{\text{Ni(H)}} CH_3CH(NH_2)CO_2H$$
$$SCH_2CH(NH_2)CO_2H$$
$$\text{LXVI}$$
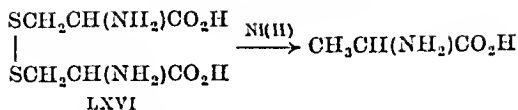
The reaction between a mixture of diphenyl disulfide (LXVII) and 2,2'-dinaphthyl disulfide (LXVIII) in the presence of degassed (200°) Raney nickel at 220° illustrates the consequences of a limited hydrogen supply.[11] This reaction also illustrates the cross coupling that would be predicted on the basis of a free-radical mechanism.

$$(C_6H_5S{-})_2 + 2,2'\text{-}(C_{10}H_7S{-})_2 \rightarrow$$
$$\text{LXVII} \qquad\qquad \text{LXVIII}$$

$$\qquad\qquad 2,2'\text{-}(C_{10}H_7)_2 + 2\text{-}C_6H_5C_{10}H_7 + (C_6H_5)_2 + C_6H_6$$
$$\qquad\qquad\quad 32\% \qquad\qquad 23\% \qquad\quad 9\% \qquad \text{trace}$$
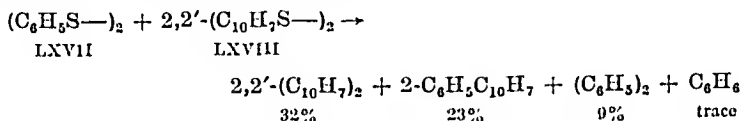
Hemithioacetals and Hemithioketals

All the examples of hemithioacetal desulfurization are drawn from carbohydrate chemistry, a circumstance which reflects the ready preparation of this type of derivative from the saccharides. In every case, sulfur was removed from the hemithioacetal without disturbing the carbon-oxygen bond.

$$\begin{array}{c} R' \\ | \\ RO{-}C{-}SR''' \\ | \\ R''(H) \end{array} \xrightarrow{\text{Ni(H)}} \begin{array}{c} R' \\ | \\ RO{-}CH \\ | \\ R''(H) \end{array}$$
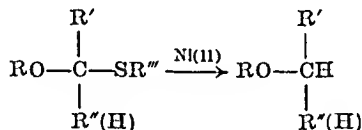
Ribose, as the tribenzoate of the 2-naphthylthiopyranoside (LXIX), is one of several pentoses and hexoses that have been converted to anhydrosugar alcohols.[105] Other examples demonstrate that the alcoholic hydroxyl groups need not be protected during the desulfurization

LXIX
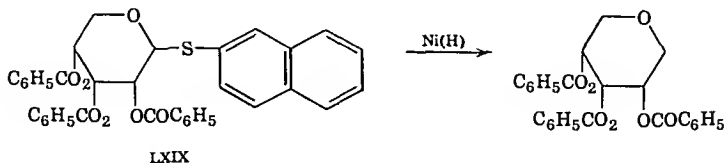
process.[106, 107] The method is equally successful with disaccharides. For example, the maltose derivative LXX gave rise to the expected product in 78% yield.[108]

[105] Jeanloz, Fletcher, and Hudson, *J. Am. Chem. Soc.*, **70**, 4052 (1948).
[106] Fletcher, Koehler, and Hudson, *J. Am. Chem. Soc.*, **71**, 3679 (1949).
[107] Huebner and Link, *J. Biol. Chem.*, **186**, 387 (1950).
[108] Buu-Hoï and Sy, *Compt. rend.*, **242**, 2011 (1956).
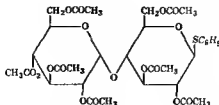
The structure of streptobiosamine, a major portion of the streptomycin molecule, was elucidated by desulfurization of the sulfur derivative LXXI to the bisdeoxy compound LXXII whose hydrolysis products were subsequently identified When the thiostreptobiosamide LXXI was heated with aged (rather than freshly prepared) nickel, the terminal formyl group was regenerated.[109]
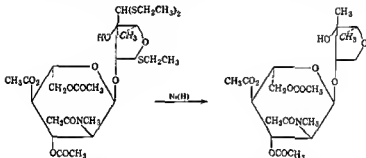
The first instance of hemithioketal desulfurization involved the cholanic acid derivative LXXIII,[110] while the first example of carbonyl
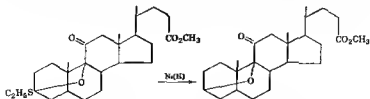
[109] Kuehl, Flynn, Brink, and Folkers J Am. Chem Soc., 68, 2096 (1946)
[110] Fieser, Heymann, and Rajagopalan, J Am. Chem Soc., 72, 2306 (1950), 73, 5252 (1951).

regeneration from a hemithioketal was provided by LXXIV.[111] Desulfurization of androst-4-ene-3,17-dione 17-ethylenehemithioketal (LXXIV) gave the original diketone LXXV. It appeared likely that the

LXXIV   LXXV
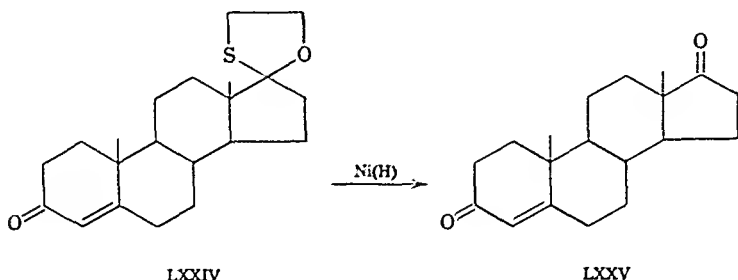
diketone LXXV might arise through collapse of a free-radical intermediate LXXVI.[111] However, subsequent work by Djerassi and collaborators[45, 46]
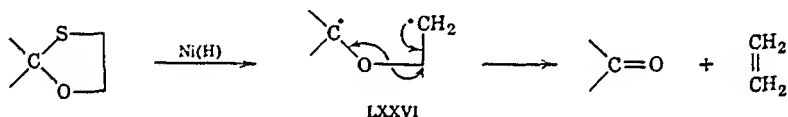
LXXVI

clearly shows that oxygen may have been introduced from another source. Three of the four possible diastereoisomeric forms of spiro-(5-benzhydryl-1,3-oxathiolane-2,3'-cholestane) were isolated and the isomer designated A (LXXVII), upon desulfurization in methyl ethyl ketone solution, gave cholestan-3-one (LXXVIII), (+)-1,1-diphenylpropan-2-ol (LXXIX), and cholestan-3β-ol. Isomer C (LXXVII), in a similar experiment, afforded the ketone LXXVIII in 80% yield accompanied by (−)-1,1-diphenyl-

$(C_6H_5)_2CH$ LXXVII   LXXVIII 78%

HO   2%   + (+)-$(C_6H_5)_2CHCH(OH)CH_3$ LXXIX 52%
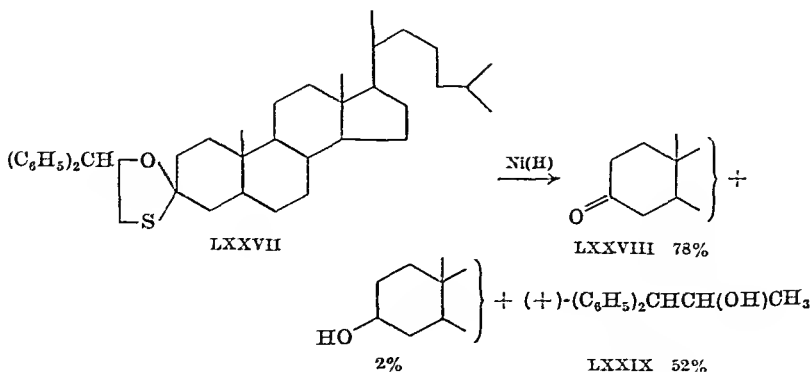
propan-2-ol (57%).[45] Analogous results have been obtained with other cyclic hemithioketals and Raney nickel in polar solvents (alcohols and ketones).[41-46]

The total yield of oxygenated products demonstrates the introduction of oxygen during desulfurization, whereas preservation of asymmetric centers (e.g., LXXXII) indicates both loss of the ketone oxygen during hemithioketal formation and cleavage of the oxygen-carbon steroid bond during hydrogenolysis.[45]

A possible mechanism[45] for the "oxygen introduction" step has been suggested After formation of a coordinate bond between sulfur and nickel, an intermediate such as LXXX might be available for attack by

LXXX   LXXXI

$$C=O + RCH(OH)CH_3$$
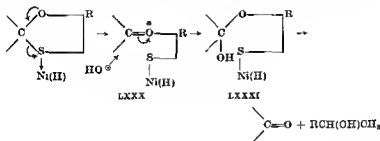
hydroxide ion (from the catalyst) to yield a hemketal (LXXXI). The ketone and alcohol fragments could then arise after desulfurization (via the usual free-radical pathway) and cleavage of the hemketal (LXXXI) The latter step might take place during isolation[45]

When desulfurization of a hemithioketal is allowed to occur in a non-polar solvent, such as benzene, the reaction follows a more complex

LXXXII

$(C_6H_5)_2CHCH(C_6H_5)O$ 24-36%

$+ (C_6H_5)_2CHCH(OH)C_6H_5$ 17-22%

$+ (C_6H_5)_2CH(CH_2)_2CH_3$ 21-29%

45-56%
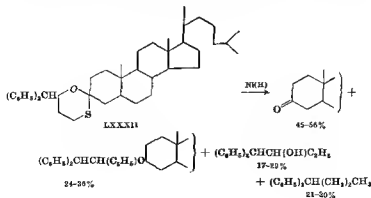
course. For example, spiro-(6-benzhydryl-1,3-oxathiane-2,3'-cholestane)
(LXXXII) led to the compounds shown in the accompanying formulation.
The formation of these products probably proceeds from a free-radical
intermediate such as LXXVI above.[46]

The experiments described above have practical significance because
isolated ketonic carbonyl groups can be converted preferentially to
hemithioketals in the presence of α,β-unsaturated ketone functions and
the reaction can be reversed simply with Raney nickel.

Dithioacetals and Dithioketals

Since dithioacetals (mercaptals) and dithioketals (mercaptols) can be
hydrogenolyzed smoothly with Raney nickel, a route other than Clem-
mensen or Wolff-Kishner reduction is available whereby an aldehyde or
ketone carbonyl group can be transformed into a methyl or methylene
group. The desulfurization route is preferable on occasion because the
reaction can be carried out in almost neutral media.
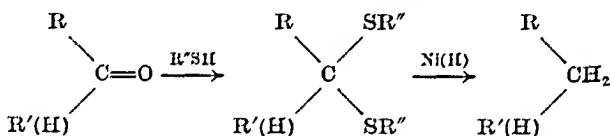
The first account of thioacetal and thioketal desulfurization was
published in 1944 by Wolfrom, who obtained, for example, toluene and
n-heptane in good yields from the ethyl mercaptan derivatives of benzalde-
hyde and heptanal or 2-heptanone, respectively.[8] The sequence has
since been applied also to α- and β-keto esters,[112] and 1,3-cyclobutane-
diones;[31,113] a specific example is the synthesis of the dicarbethoxy-
bicyclooctane LXXXIV from LXXXIII.[114]

Hauptman[10] has noted the behavior of mercaptols when heated in
xylene with degassed Raney nickel. Those derived from benzaldehyde
and from acetophenone yielded stilbenes.

LXXXIII   LXXXIV
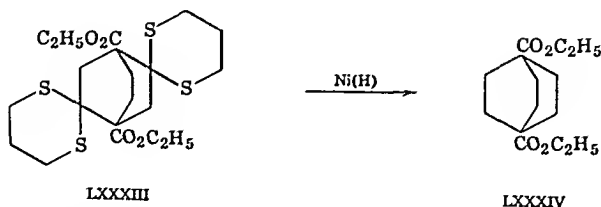
[112] Newman and Walborsky, *J. Am. Chem. Soc.*, **72**, 4296 (1950).
[113] Herzog and Buchman, *Abstracts of Am. Chem. Soc. Meeting*, Chicago, Sept. 1950, p. 31N.
[114] Roberts, Moreland, and Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953).

$$C_6H_5CH(SR)_2 \xrightarrow{Ni} C_6H_5CH=CHC_6H_5$$

$$C_6H_5C(SR)_2CH_3 \xrightarrow{Ni} C_6H_5C(CH_3)=C(CH_3)C_6H_5$$
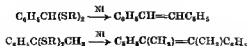
One very interesting failure to undergo hydrogenolysis has been reported. The quinazolone LXXXV was found to regenerate the parent
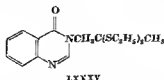
LXXXV

ketone.[115] The dithioketal LXXXVI of the yohimbine degradation product yohimbone was unchanged by Raney nickel in boiling alcohol.[116]
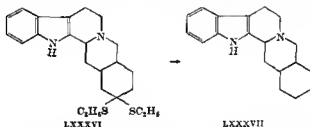
LXXXVI   LXXXVII

However, it was subsequently shown that desulfurization to yohimbane (LXXXVII) is possible when freshly prepared W-7 Raney nickel and dioxane are employed.[117]

The conversion of the ethyl dithioketal LXXXVIII to the octadeca-hydropentacene LXXXIX in 55% yield illustrates the selectivity of the reaction.[118] An unexpected C-ethylation occurred during desulfurization

LXXXVIII   LXXXIX
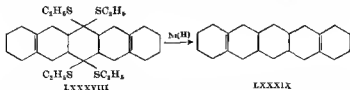
of isatin ethylenethioketal (XC) in ethanol solution. With methyl or isopropyl alcohol as solvent, the yields of similar alkylated products

[115] Hutchings, Gordon, Ablondi, Wolf, and Williams, J Org Chem., 17, 19 (1952)

[116] Groves and Swan, J. Chem. Soc., 1952, 650

[117] Rapala, Lavagnino, Shepard, and Farkas, J. Am Chem. Soc., 79, 3770 (1957).

[118] Bailey and Madoff, J Am Chem. Soc., 75, 5603 (1953)
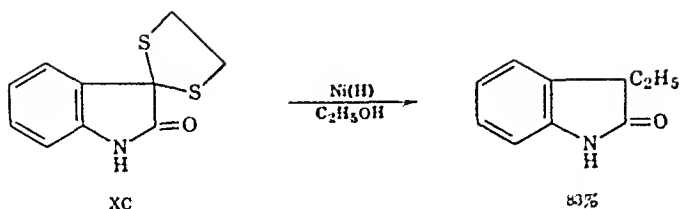
were 16% and 32%, respectively.[22] Desulfurizations of certain N-substituted pyridazinones also have been found to follow an unpredicted course. Raney nickel desulfurization of the diethylmercaptol XCI in 70% ethanol
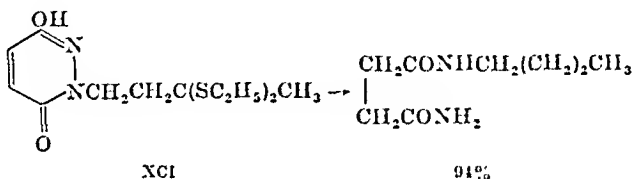
led to n-butylsuccinamide. Under the same conditions, 2-n-butyl-6-hydroxy-3(2H)-pyridazinone (XCII) formed n-butylsuccinamide in 82% yield.
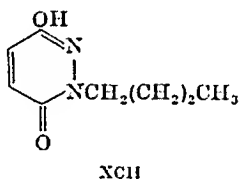
A number of deoxy sugars have been synthesized by application of the thioketal desulfurization sequence to various monosaccharides or their fully acetylated derivatives. The conversion of glucose pentaacetate to the deoxyglucitol (XCIII) in 60% yield was one of the first examples
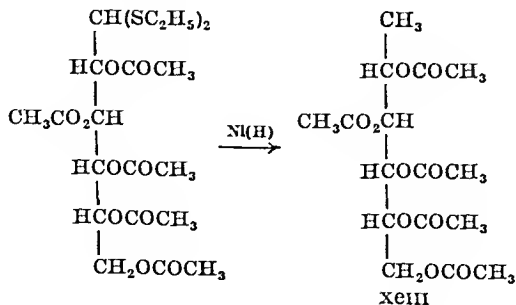
reported [8] *A lower yield (20%) was obtained in the only well-defined application to a ketose (fructose).*[8]

A decisive role has been played by mercaptol desulfurization in the structural investigation of a number of complex natural products. Of particular significance is the conversion of the strychnine transformation product methoxymethylchanodihydrostrychnone diethylmercaptol XCIV to the deoxy product XCV.[119] Earlier attempts to effect the change by

XCIV   XCV
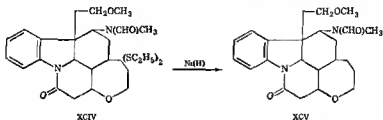
means of a Clemmensen reduction were attended by rearrangements, a result which obscured the nature of the strychnine *neo*-bases and thereby stood as an obstacle in the way of final acceptance of the correct strychnine formula.

One of the degradation procedures instrumental in elucidating the structure of the tricyclic diterpenoid rosenonolactone involved desulfurization of the ethylenethioketal XCVI.[120]

XCVI

An attempt to utilize the boron trifluoride procedure[121] for the preparation of ethylenethioketals in the steroidal sapogenin series produced an interesting structural problem Ethanedithiol in the presence of boron trifluoride etherate was found to react with the spiroketal system. Exact knowledge of the skeletal change which had taken place remained unknown until Raney nickel desulfurization of the compound subsequently shown

[118] Woodward and Brehm, *J. Am. Chem. Soc*, **70**, 2107 (1948).

[119] Harris, Robertson, and Whalley, *J. Chem Soc*, 1958, 1799.

[120] Fieser, *J. Am Chem. Soc*, **76**, 1945 (1954).

XCVII   75%
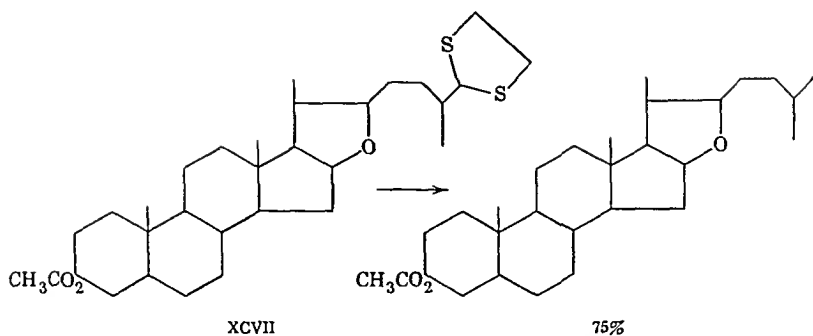
to be 5α-furostan-3β-ol acetate 26-ethylenethioketal (XCVII) provided
5α-furostan-3β-ol acetate, an intermediate of known structure.[122]

The steroid literature is replete with examples of the reaction under
discussion. Carbonyl groups at positions 2, 3, 6, 7, 12, 15, 16, 17, and
19 on the steroid nucleus have been converted to methylene groups; no
desulfurization failures have been reported.

The following experiment is one of many that demonstrate the selective
nature of the Raney nickel desulfurization reaction. Desulfurization of
the 12-trimethylenethioketal XCVIII was accomplished in 86% yield by

XCVIII
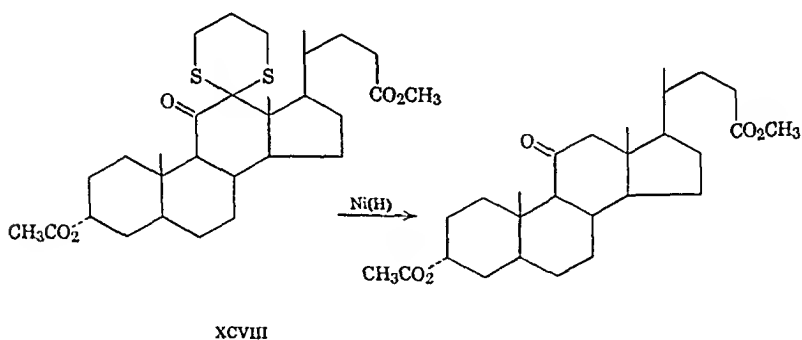
allowing the reaction to proceed for 15 minutes at room temperature.
Extending the contact time to 6 hours raised the yield to 95%.[123]

Olefin bonds need not interfere (cf. the isolation of 4-cholestene in 92%
yield by the desulfurization of 4-cholesten-3-one dibenzylmercaptol).[77]
However, the choice of experimental conditions is usually quite important,
as for example in the desulfurization of cholest-1-ene 3-ethylenethioketal
(XCIX). Hydrogenolysis in refluxing benzene-methyl ethyl ketone

[122] Djerassi, Halpern, Pettit, and Thomas, J. Org. Chem., 24, 1 (1959).
[123] Archer, Lewis, Martini, and Jackman, J. Am. Chem. Soc., 76, 4915 (1954).

solution over a 9-hour period gave a fair yield of cholest-2-ene.[124]   When the thioketal XCIX was subjected to a 40-hour reaction period, in boiling dioxane, only cholestane was isolated.[125]

XCIX
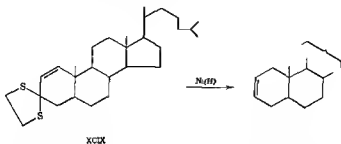
Treatment of the 7-ketocholesterol derivative C with deuterized Raney nickel resulted in the formation of 7,7-d$_2$-cholesterol (CI).[126]   This is one

C   CI
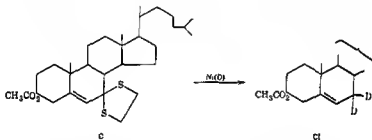
of several examples of the introduction of deuterium by means of Raney nickel

The action of aged nickel in refluxing dioxane on the ketol derivative CII gave hydrogenolysis accompanied by oxidation at C.17;[12] production

CII
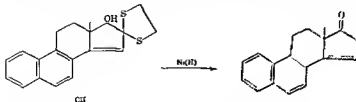
[124] Striebel and Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).
[125] Plattner, Fürst, and Els, *Helv. Chim. Acta*, **37**, 1399 (1954).
[126] Fukushima, Lieberman, and Praetz, *J. Am. Chem. Soc.*, **72**, 5205 (1950).

of the hydroxyl group by acetylation prevents this interesting side reaction.[32,127,128] In a somewhat similar vein, the spirostene derivative CIII led to the C-11 ketone,[129] an intermediate in a synthetic approach to cortisone.

CIII
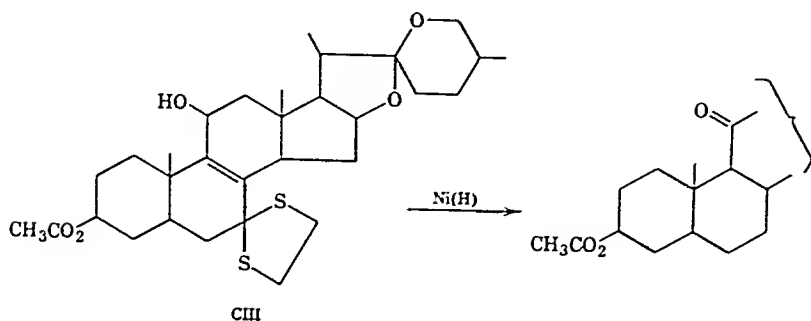
Similar conversions have been conducted with several triterpenoids and lanosterol derivatives. Interestingly enough, the mono dithioketal of acetoxylanostendione (CIV) afforded the β,γ-unsaturated ketone CV,

CIV   CV
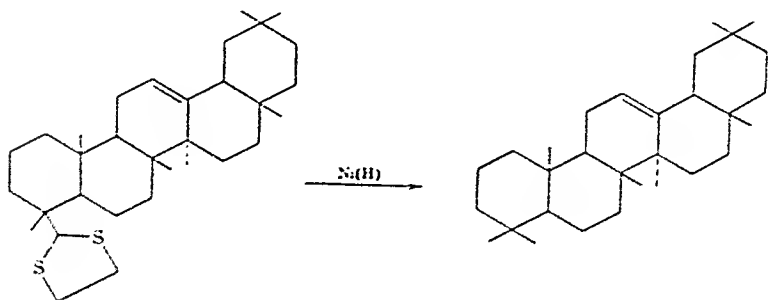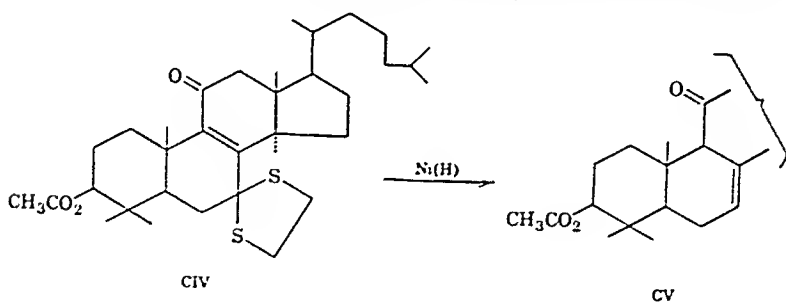
rather than the α,β-unsaturated ketone on desulfurization.[130] Oleanolic acid, after reduction to the aldehyde followed by conversion to the ethylenethioketal and desulfurization, gave 12,13-oleanene (CVI).[131] The ethylenethioketal CVII, a derivative of the cactus triterpene dumortierigenin, was also readily reduced without affecting the remaining portion of the molecule.[132]

CVII
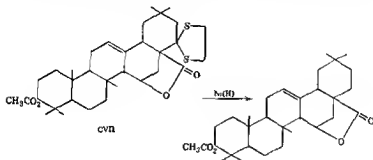
Thioamides

Desulfurization of thioamides can take divergent courses, depending upon the nature of the Raney nickel. Partial deactivation carried out in boiling acetone affords a reagent that will convert a thioamide to an aldehyde in good yield.[133] Raney nickel as ordinarily prepared, however,

$$\underset{\parallel}{\overset{S}{RCNHR'}} \xrightarrow{Ni(H)} RCHO$$

brings about replacement of thiocarbonyl by methylene groups.[27] A relatively large number of transformations of the latter type have been

$$\underset{\parallel}{\overset{S}{RCNR'R''}} \xrightarrow{Ni(H)} RCH_2NR'R''$$
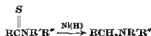
carried out by Kornfeld,[27] who varied considerably the nature of R, R', and R''. Extended heating of certain amides in ethanol with Raney nickel led to replacement of the N-alkyl group by an ethyl group, e.g., the benzyl

[130] Mijović, Voser, Heusser, and Jeger, *Helv. Chim. Acta*, **35**, 964 (1952).
[131] Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, **34**, 2321 (1951).
[132] Djerassi, Robinson, and Thomas, *J. Am. Chem. Soc.*, **78**, 5685 (1956).
[133] Cronyn and Goodrich, *J. Am. Chem. Soc.*, **74**, 3936 (1952).

thioamide shown in the accompanying formula gave a 44% yield of
N-ethylpiperidine.[27, 33]

$$C_6H_5CH_2CSN \text{\large$\bigcirc$} \xrightarrow[C_2H_5OH]{Ni(H)} C_2H_5N \text{\large$\bigcirc$}$$
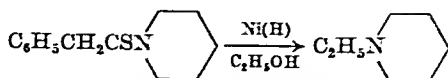
In all the thiourea desulfurizations reported, formamidines have been
the observed products.[62, 134] Even thiosemicarbazones conform to this
reaction pattern.[135]

$$C_6H_5CH{=}NNHCSNH_2 \xrightarrow{Ni(H)} C_6H_5CH{=}N{-}N{=}CHNH_2$$
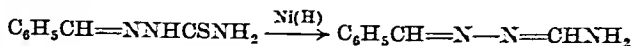
Among heterocyclic thioamides, study of thiohydantoins and thio-
barbituric acids has received major emphasis. Generally, desulfurization
in ethanol solution (2–5 hours at reflux) results in replacement of sulfur
by hydrogen. The desulfurization of 5,5-diphenyl-2-thiohydantoin
(CVIII)[136, 137] and 5-ethyl-5-phenyl-2-thiobarbituric acid (CIX)[133] may be
considered illustrative.

CVIII   64–85%

CIX
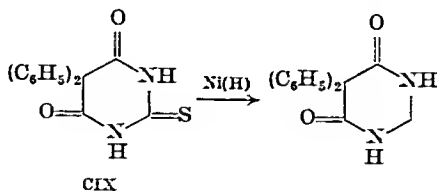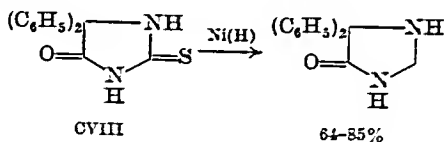
Several experimental variations have been reported, the results of
which provide a more comprehensive picture of the normal desulfurization
process. Addition of sodium ethoxide to an ethanol solution of the

75%
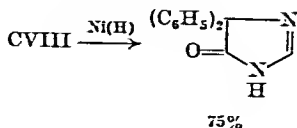
[134] Brown, J. Applied Chem. (London), 2, 202 (1952).
[135] Hoggarth, J. Chem. Soc., 1951, 2202.
[136] Carrington, Vasey, and Waring, J. Chem. Soc., 1953, 3105.
[137] Behringer and Schmeidl, Chem. Ber., 90, 2510 (1957).
[133] Boon, Carrington, Greenhalgh, and Vasey, J. Chem. Soc., 1954, 3263.

thiohydantoin CVIII apparently allows the tautomeric thiol form to undergo desulfurization without further reduction.[139] The same result may be achieved by using a limited quantity of catalyst.[140] With a 30-minute reflux period and a 1:5 ratio by weight of thioamide CVIII to Raney nickel, approximately equal amounts of 5,5-diphenyl-4-imidazolidone (CX) and di-2-(4,4-diphenyl-5-oxo-2-imidazolinyl) sulfide (CXI) were formed. A small quantity of 5,5-diphenyl-2-hydroxy-4-imidazolidone (CXII) was also isolated.[141] Upon further treatment (2 hours in
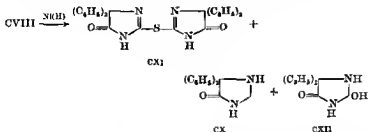
boiling ethanol) with Raney nickel, the hydroxyl compound CXII is reduced to the imidazolidone CX in quantitative yield.[141] The tendency to form 2-hydroxy derivatives analogous to CXIII becomes quite evident with the cyclohexyl derivative CXIV.[138] The tetrasubstituted thio-

hydantoin CXV, in ethanol solution, has been found to yield a 2-ethoxy derivative Substitution of methanol, 1-propanol, or cyclohexane for
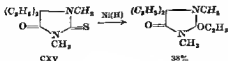
[139] Sprštíl, *Chem Listy* 47, 1785 (1953) [C.A. 49, 1029 (1955)].
[140] Staněk and Šilo, *Chem Listy*, 47, 89 (1953) [C.A. 48, 2857 (1954)].
[141] Whalley, Anderson, DuCasse, Wilson, and Ullyott, *J. Am Chem. Soc.*, 77, 745 (1955).

ethanol produced the 2-hydroxy derivative.[136]   However, it was possible
to prepare a series of 2-alkoxy derivatives (e.g., CXVI) of the thio-

$$\text{CIX} \xrightarrow[\text{CH}_2(\text{CH}_2)_2\text{CH}_2\text{OH}]{\text{Ni(R)}}$$

(image of CXVI structure)

CXVI
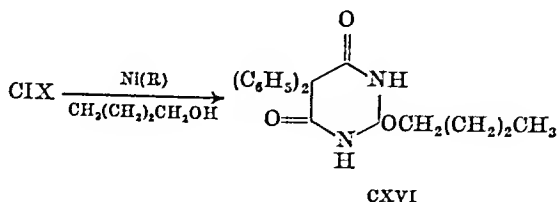
barbituric acid CIX by limiting the reaction period to 30 minutes.
Quantitative reduction to the normal desulfurization product resulted
from further treatment with Raney nickel.[141]   Formation of hydroxy and
alkoxy intermediates such as CXII and CXVI has been attributed to one
of two possible mechanistic routes (cf. CXVII and CXVIII where Y equals
the remaining portion of the ring).[141]

(reaction scheme with CXVII and CXVIII)

CXVII

CXVIII
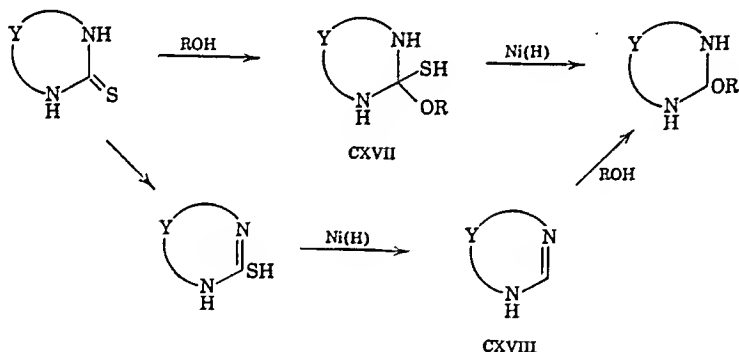
Desulfurization of 5-monosubstituted-2-thiobarbituric acids leads to the
conclusion that these compounds are perhaps better represented as
reacting through a tautomeric 2-pyrimidinethiol structure (cf. CXIX)
since the product is invariably a 4,6-dihydroxypyrimidine.[141]

(reaction scheme CXIX)

CXIX
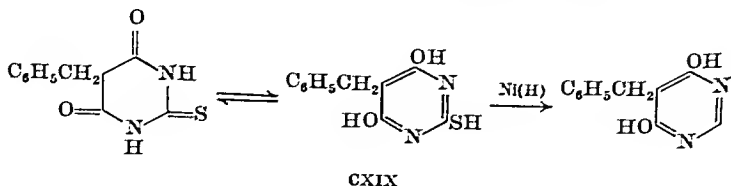
A series of 5-alkylidene- and 5-benzylidene-2-thiohydantoins, such as
CXX, has been found to yield α-formylamino acid amides when de-
sulfurization is carried out in aqueous tetrahydrofuran. The reaction
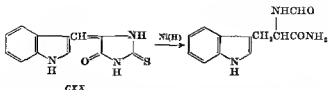
should find practical application as a route to α-amino acids.[137] Desulfurization of 3,4,5-triphenyloxazole-2-thione (CXXI)[142] in ethanol apparently proceeds by a similar mechanistic pathway
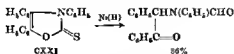
Thiol Esters

When the reductive desulfurization of a thiol ester is considered only in terms of bond cleavage between the sulfur atom and the alkyl or aryl, rather than the carbonyl, carbon atom, no particular problem arises simple hydrogen–carbon bond formation occurs as in the numerous cases already cited. Cysteine and alanine have been interrelated stereo-

$$R\!-\!S\!-\!\overset{\overset{\displaystyle O}{\|}}{C}\!-\!R' \xrightarrow{\text{N(H)}} R\!-\!H$$
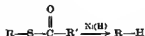
chemically by carrying out a desulfurization on the S-benzoyl-N-phthaloyl
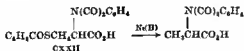
derivative CXXII of the former.[143] The conversion of the acetate-thioacetate CXXIII to the expected monohydric alcohol CXXIV is
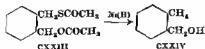
representative of a number of closely related transformations in the cyclohexane series[144]

---

[137] Compare ref. 437
[142] Fišer and Balenović, *J Chem Soc*, 1952, 2447
[143] Haggis and Owen, *J Chem Soc* 1953, 408

The consequences of limiting the supply of available hydrogen during desulfurization of thiol esters have been explored.[11] The reaction

$$C_6H_5COSC_6H_5 \rightarrow C_6H_5C_6H_5 + C_6H_5SC_6H_5$$
$$\text{CXXV} \qquad\quad 37\text{–}58\% \qquad 18\text{–}76\%$$
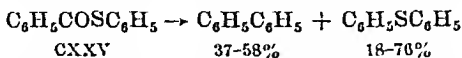
between phenyl thiobenzoate (CXXV) and degassed (200°) Raney nickel, at either 180° or 220° in xylene solution, provides an example.

Cleavage of the sulfur-carbonyl carbon bond produces either an aldehyde,[145] which can be considered the primary hydrogenolysis product,

$$R\!-\!S\!-\!\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}\!-\!R' \quad \begin{matrix} \nearrow \\ \\ \searrow \end{matrix} \quad \begin{matrix} H\!-\!\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}\!-\!R' \\ \\ HOCH_2\!-\!R' \end{matrix}$$
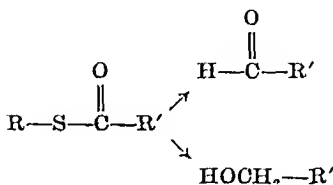
or an alcohol resulting from further reduction. Instances of the controlled cleavage were reported first by Wolfrom, who transformed ethyl thiobenzoate and ethyl thiopropionate into benzaldehyde and propionaldehyde, respectively, in good yield, but did not define exactly the nature of the nickel used.[146] Somewhat later, Spero, McIntosh, and Levin[147] noted that the character of the reagent was of importance and demonstrated that good yields of aldehydes, such as the diformoxycholanal CXXVI, could be obtained provided the nickel was first *partially* deactivated by heating briefly in boiling acetone; failure to observe this
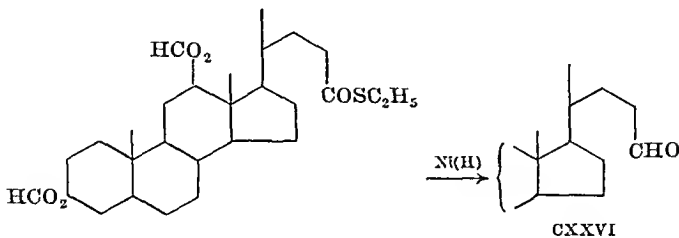
expedient usually resulted in reduction to the alcohol. Aldehyde formation by this process has been successful with a number of other steroids. In addition, succinaldehyde[148] and 2,2-dimethyl-3-carbomethoxycyclopropanecarboxaldehyde[149] have been obtained by using this technique.[149a]

[145] Mosettig. in Adams, *Organic Reactions*, Vol. VIII, p. 229, Wiley. New York. 1954.
[146] Wolfrom and Karabinos, *J. Am. Chem. Soc.*, 68, 724, 1455 (1946).
[147] Spero, McIntosh, and Levin, *J. Am. Chem. Soc.*, 70, 1907 (1948).
[148] King, Hofmann, and McMillan, *J. Org. Chem.*, 16, 1100 (1951).
[149] Harper and Reed, *J. Sci. Food Agr.*, 2, 414 (1951) [*C.A.*, 46, 9066 (1952)].
[149a] Ref. 441 describes an improved procedure.

However, the piperidyl thiopropionate CXXVII has been reported only to cyclize to the lactam under desulfurization conditions,[148] and 3,4,5-trimethoxybenzaldehyde apparently cannot be obtained from thiol esters of O-trimethylgallic acid.[150,150a]

CXXVII

A *novel observation is the production* of 1-indanone (CXXVIII) from 1,2-dihydro-1-keto-2-thianaphthalene (CXXIX).[151] It has been
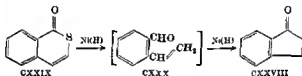
suggested[151] that the initial product is o-vinylbenzaldehyde (CXXX), which is known to cyclize to 1-indanone.

Just as the method described above constitutes a means of transforming an acid into the corresponding aldehyde, desulfurization of a thiol ester by ordinary (not acetone-deactivated) nickel allows the selective, over-all reduction of an acid to an alcohol. Various simple thiol esters, such as benzyl thiobenzoate or methyl thiopalmitate, yielded the expected alcohols,[152] beyond this, *one* carboxyl of a dibasic acid, e.g., adipic acid,[152] can be reduced to carbinol by carrying out the desulfurization on a monothiol ester. Alanine has been reduced via the methyl thioester to optically active 2-aminopropanol.[153] An illustration of reduction as a side reaction is one involving the nitro group in benzyl 3-nitro-2-methylthiobenzoate (CXXXI).[47]
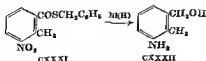
[150] Frank, Fanta, and Tarbell, *J Am Chem Soc.*, 70, 2314 (1948).

[150a] Cook, Dickson, Jack, London, McKeown, McMillan, and Williamson, *J Chem Soc.*, 1950, 139.

[151] Dijayman and Newbold, *J Chem Soc.*, 1932, 13.

[152] Mozingo, U.S. pat. 2,457,392, 1948 [*C A.*, 43, 2644 (1949)].

[153] Jager, Norymberski, Sapiñogel, and Freeg, *Helv Chim Acta*, 29, 684 (1946).

A number of thiol esters of steroids have been converted to primary alcohols.[154] Double bonds and carboxylic ester functions usually remain undisturbed. However, interaction of a carbomethyoxl group is illustrated in the desulfurization of the etiobilienic thiol ester CXXXIII, which led to the δ-lactone CXXXIV.[155, 156] The transformation of benzyl 12,13-oleanen-

CXXXIII → Ni(H) → CXXXIV
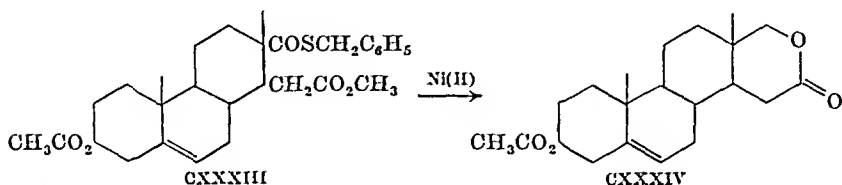
30-thiolate (CXXXV) into the oleanenol CXXXVI[157] is one of a number of cases reported in the terpene field.

CXXXV → Ni(H) → CXXXVI
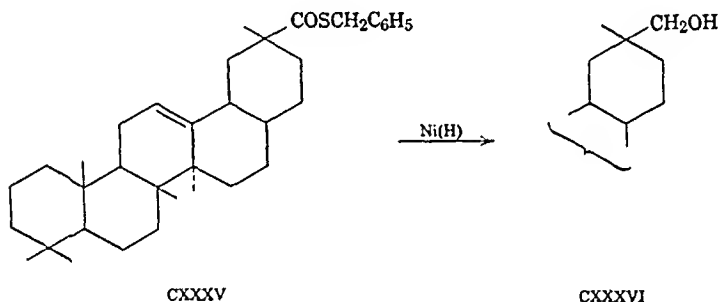
Isothiouronium Salts

Although the fate of the thiourea portion of an isothiouronium salt during desulfurization has not been reported, the alkyl group attached to sulfur is hydrogenolyzed. The salt obtained by treatment of 1,8-di(bromomethyl)anthracene with thiourea was transformed in good yield

CXXXVII → Ni(H) →
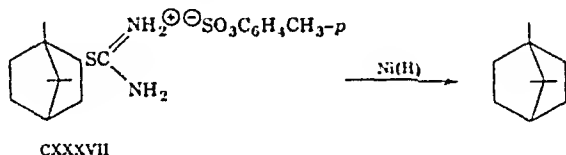
into 1,8-dimethylanthracene.[158] Isobornyl isothiouronium p-toluene-sulfonate (CXXXVII) gave camphane without skeletal rearrangement[159]

Thiophenes and Thiazoles

Inclusion of sulfur in an aromatic nucleus does not preclude hydrogenolysis. Preliminary evidence of this was recognized as early as 1940 when Bougault[160] reported the preparation of thiophene-free benzene and toluene by desulfurization with Raney nickel. The desulfurization of thiophene derivatives has since received wide application as a synthetic route to a variety of compounds

The possibility of using substituted thiophenes as precursors to more difficultly accessible long-chain aliphatic compounds has led to more work on the desulfurization of thiophenes than of any other group of compounds. Notable is the recent work of Badger,[14,79,161–164] Buu-Hoi,[128,136,165–172] Gol'dfarb,[34,48,173–184] and Wynberg.[128,166] By early 1960 Raney nickel desulfurization of approximately 190 thiophenes had been

158 Badger, Campbell, Cook, Raphael, and Scott, J Chem Soc, 1950, 2326
159 Shibukawy and Kung, J Am Chem Soc, 73, 7647 (1951)
160 Bougault, Cattelain, and Chabrier, Bull soc chim France, [5] 7, 780 (1940)
161 Badger, Australian J Sci, in press
162 Badger, Christie, Pryke, and Sasse, J Chem Soc, 1957, 4417
163 Badger, Christie, Pryke, and Sasse, J Chem Soc, 1959, 440
164 Badger, Kowanko, and Sasse, J Chem Soc, 1954, 4162
165 Badger, Rodda, and Sasse, J Chem Soc, 1954, 4162
166 Buu Hoi, Nature, 180, 283 (1957)
167 Buu Hoi, Sy, and Xuong, Compt rend, 240, 785 (1955)
168 Buu Hoi, Sy, and Xuong, Compt rend, 240, 442 (1955)
169 Buu Hoi, Sy, and Xuong, Bull soc chim France, 1955, 1583
170 Buu Hoi, Sy, and Xuong, Rec trav chim, 75, 463 (1956)
171 Sy, Buu Hoi, and Xuong, J Chem Soc, 1954, 1975
172 Sy, Buu Hoi, and Xuong, J Chem Soc, 1955, 1224 (1954)
173 Sy, Buu Hoi, and Xuong, Compt rend, 239, 1813 (1954).
174 Gol'dfarb and Danyushevskii, Izvest Akad Nauk S.S.S.R., Otdel Khim Nauk, 1956,
1361 [C A , 51, 3065 (1957)]
175 Gol'dfarb and Fabrichnyi, Doklady Akad Nauk S.S.S.R., 100, 461 (1955) [C A , 49,
8244 (1955)]
176 Gol'dfarb, Fabrichnyi, and Shalavina, Zhur. Obshchei Khim., 26, 2595 (1956) [C A , 51,
4943 (1957)]
177 Gol'dfarb, Fabrichnyi, and Shalavina, Doklady Akad Nauk S.S.S.R., 106, 490 (1956) [C A , 51,
12838 (1957)]
178 Gol'dfarb and Ibragimova, Doklady Akad Nauk S.S.S.R., 113, 594 (1957) [C A , 51,
13062 (1957)]
179 Gol'dfarb and Ibragimova, Doklady Akad Nauk S.S.S.R., 113, 1373 (1955) [C A , 50, 6422 (1956)]
180 Gol'dfarb and Kirmalova, Zhur Obshchei Khim., 25, 1373 (1955) [C A , 50, 6422 (1956)]
181 Gol'dfarb and Kirmalova, Izvest. Akad. Nauk S.S.S.R., Otdel Khim Nauk, 1955, 570
[C A , 50, 6422 (1956)]
182 Gol'dfarb and Kirmalova, Izvest. Akad. Nauk S.S.S.R., Otdel Khim Nauk, 1957, 479
[C A , 51, 16490 (1957)]

Raney nickel hydrogenolysis of thiophene hydrocarbons (CXXXVIII),[173] acetals (CXXXIX),[152] alcohols (CXL),[175] ketones (CXLI),[154] acids

CXXXVIII

$CH_3(CH_2)_{13}CH_3$

59%

CXXXIX

$CH_3(CH_2)_3CH(OC_2H_5)_2$

50%

CXL

50%
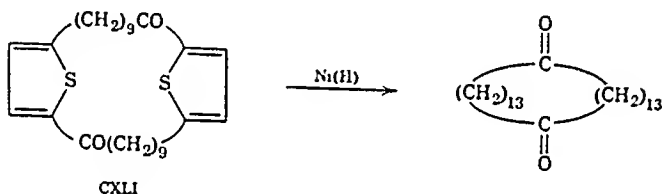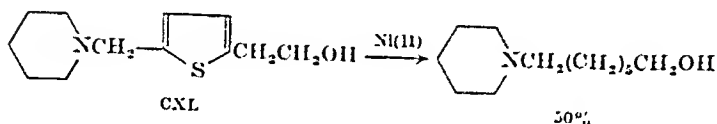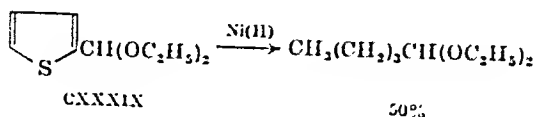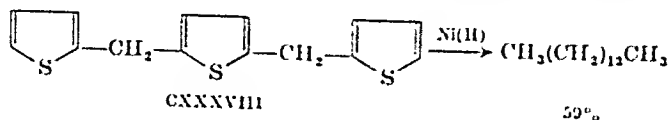
CXLI

(CXLII),[161,187,187a] and amino acids (CXLIII)[175] usually does not present any special difficulty. The examples given represent the normal path of thiophene desulfurization and emphasize several practical applications.

[152] Gol'dfarb and Konstantinov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk,* 1957, 217 [*C.A.,* 51, 10474 (1957)].

[153] Gol'dfarb and Korsakova, *Doklady Akad. Nauk. S.S.S.R.,* 96, 283 (1954) [*C.A.,* 49, 5430 (1955)].

[154] Gol'dfarb, Taits, and Belen'kiĭ, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk,* 1957, 1262 [*C.A.,* 52, 6310 (1958)].

[154a] Gol'dfarb, Polonskaya, Fabrichnyĭ, and Shalavina, *Doklady Akad. Nauk S.S.S.R.,* 126, 86 (1959) [*C.A.,* 53, 21872 (1959)].

[154b] Gol'dfarb and Konstantinov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk,* 1959, 121 [*C.A.,* 53, 16103 (1959)].

[154c] Gol'dfarb, Fabrichnyĭ, and Shalavina, *Zhur. Obshcheĭ Khim.,* 29, 891 (1959).

[154d] Gol'dfarb and Kirmalova, *Zhur. Obshcheĭ Khim.,* 29, 897 (1959).

[154e] Gol'dfarb, Taits, and Belen'kiĭ, *Zhur. Obshcheĭ Khim.,* 29, 3564 (1959).

[154f] Gol'dfarb, Fabrichnyĭ, and Shalavina, *Zhur. Obshcheĭ Khim.,* 29, 3636 (1959).

[155] Wynberg and Logothetis, *J. Am. Chem. Soc.,* 78, 1958 (1956).

[156] Wynberg, Logothetis, and Ver Ploeg, *J. Am. Chem. Soc.* 79, 1972 (1957).

[157] Diaper and Kuksis, *Chem. Revs.,* 59, 89 (1959).

[157a] Grey, McGhie, and Ross, *J. Chem. Soc.,* 1960, 1502.

$$HO_2C \underset{\overset{\displaystyle S}{}}{\overset{\displaystyle CH_3}{\bigcirc}}-C\underset{CH_3}{\overset{CH_3}{|}}-\underset{\overset{\displaystyle S}{}}{\bigcirc}CO_2H \rightarrow HO_2C(CH_2)_4C(CH_3)_2(CH_2)_4CO_2H$$

CXLVI   92%

$$H_3C\underset{\overset{\displaystyle S}{}}{\bigcirc}CH(NH_2)CO_2H \xrightarrow{Ni(H)} CH_3(CH_2)_4CH(CH_2CH_3)CH(NH_2)CO_2H$$

CXLIII   51%
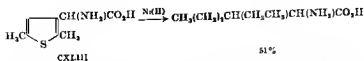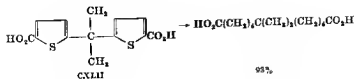
Buu-Hoï has recently prepared deuterium-labeled[138] and tritium-labeled[135] carboxylic acids by subjecting the appropriate thiophene derivative to Raney nickel desulfurization in deuterated or tritiated water. The catalyst was prepared *in situ* from Raney nickel alloy. Tuberculo-stearic acid (CXLIV, T = tritium), labeled at four positions with tritium, provides an example.

$$CH_3(CH_2)_3CH(CH_2)_3CH_3 \underset{\overset{\displaystyle S}{}}{\bigcirc}CH_2(CH_2)_3CO_2H \xrightarrow{N(T)}$$

$$CH_3(CH_2)_3CH(CT_2H)CH_2CT_2(CHT)CT_2$$

$$HO_2C(CH_2)_6$$

CXLIV
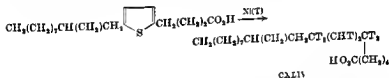
As illustrated above, removal of sulfur is usually accompanied by saturation of the annular double bonds. Unsaturation in an adjacent benzenoid system is almost always retained. One exception to the latter generalization involved the thiafluorene CXLV which was reduced to an octahydro-1-phenylphenanthrene, presumably CXLVI.[53] Limited amounts of Raney nickel have been used to remove bromine[139] or reduce

CXLV   CXLVI
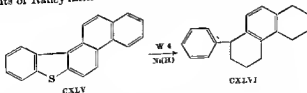
nitro groups[190, 191] without affecting the thiophene nucleus. Only a few isolated failures of desulfurization were reported, and two of these involved

[138] Buu-Hoï and Xuong, *Compt rend.*, **247**, 654 (1958)
[135] Martin Smith and Gates, *J Am Chem Soc*, **78**, 6177 (1956)
[190] Gilman and Wilder, *J Am Chem Soc*, **78**, 2906 (1956).
[191] Martin Smith and Gates, *J Am Chem Soc*, **78**, 6351 (1956)

a 1-substituted dibenzothiophene (e.g., CXLVII).[192, 193] The trisubstituted 2,5-di-t-butyl-3-acetylthiophene (CXLVIII) also resisted desulfurization.[34]

CXLVII

CXLVIII
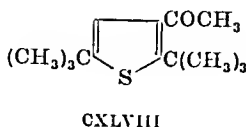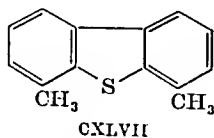
Reductions of olefin (CXLIX),[33] aldehyde (CL),[34] and oxime (CLI)[175] groups are predictable side reactions. Carbon-halogen bond hydro-

$$C_6H_5CH_2 \underset{S}{\overset{}{\bigcirc}} CH{=}C(C_6H_5)CO_2H \xrightarrow{\text{Ni(H)}} C_6H_5(CH_2)_6CH(C_6H_5)CO_2H$$

CXLIX   74%

$$(CH_3)_3C \underset{S}{\overset{CHO}{\bigcirc}} C(CH_3)_3 \xrightarrow{\text{Ni(H)}} (CH_3)_3C(CH_2)_2CH(CH_2OH)CH_2C(CH_3)_3$$

CL   58%

$$\underset{S}{\overset{}{\bigcirc}} C({=}NOH)CO_2H \xrightarrow{\text{Ni(H)}} CH_3(CH_2)_3CH(NH_2)CO_2H$$

CLI
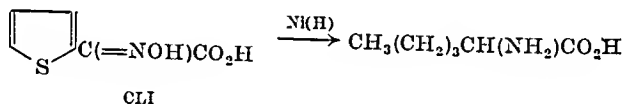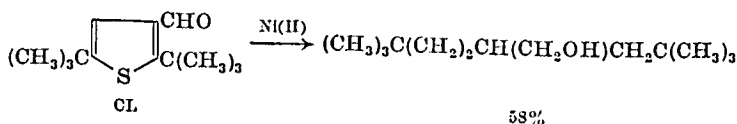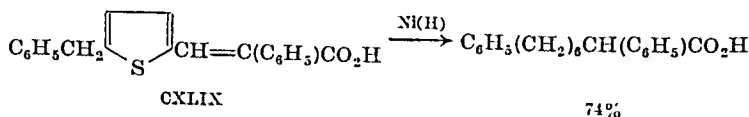
genolysis (cf., CLII)[164] is usually observed,[194] and, in a few instances, ketone to alcohol reductions have occurred.[14, 185, 187o, 195]

$$Br \underset{S}{\overset{}{\bigcirc}} CO(CH_2)_2CO_2H \xrightarrow{\text{Ni(H)}} CH_3(CH_2)_3CO(CH_2)_2CO_2H$$

CLII   25%
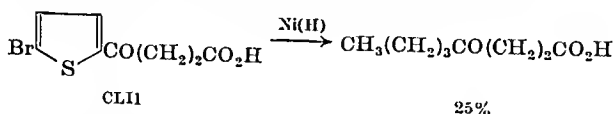
The yield and type of reaction product encountered may be markedly influenced by the choice of experimental conditions. Desulfurization of thiophene carboxylic ácid derivatives such as γ-(2,5-dimethyl-3-thienyl) butyric acid (CLIII),[163] proceeds in highest yield, in basic aqueous

$$CH_3 \underset{S}{\overset{CH_2(CH_2)_2CO_2H}{\bigcirc}} CH_3 \xrightarrow{\text{Ni(H)}} CH_3(CH_2)_2CH(C_2H_5)(CH_2)_3CO_2H$$

CLIII   CLIV 93%
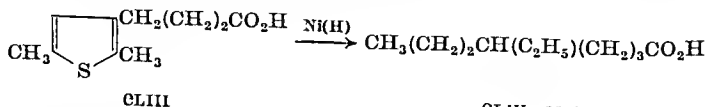
[192] Kruber and Raeithel, *Chem. Ber.*, **87**, 1469 (1954).
[193] Carruthers, *Nature*, **176**, 790 (1955).
[194] Gilman and Esmay, *J. Am. Chem. Soc.*, **75**, 2947 (1953).
[195] Wynberg and Bantjes, *J. Am. Chem. Soc.*, **82**, 1447 (1960).

solution. Only a 41% conversion to the saturated acid CLIV was realized when an organic solvent was used.

Although the thiophene CLV afforded bibenzyl when desulfurized in methanol, 1,2,3,4-tetraphenylcyclobutane resulted when the reaction was carried out in ethanol.[13] The latter product apparently arises by coupling two bibenzyl diradicals.

CLV
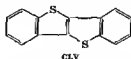
A deactivated catalyst leads to increased production of dimeric product. Desulfurization of 2-benzoylthiophene (CLVI) with a deactivated W-7 Raney nickel in methanol illustrates this side reaction [14]

CLVI	$CH_3(CH_2)_3COC_6H_5$ +	$C_6H_5CO(CH_2)_6COC_6H_5$
	47–92%	0 8–44%
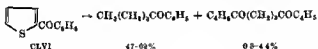
In every case studied, recombination of radicals has involved union at the unsubstituted terminal carbon of the thiophene ring, while 2,5-disubstituted thiophenes fail to yield dimeric products In view of these observations, Badger has suggested that the desulfurization mechanism involves a 2,5-diradical (i.e., CLVII). Since steric hindrance by the R

$$RC=CH-CH=CH.$$

CLVII
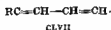
group would be relatively unimportant in solution, the diradical probably undergoes dimerization while still adsorbed on the catalyst surface.[14, 24i]

The greater resistance to desulfurization encountered with thiazoles has been attributed to competition between sulfur and nitrogen for the catalyst surface.[44]

The nature of the products derived from thiazoles appears to depend on the experimental conditions For example, 2-amino-4-phenylthiazole (CLVIII) gave acetophenone as the main product,[43] whereas 2-amino-4-hydroxythiazole[45] yielded either acetamide[45] or its N-formyl

CLVIII → $C_6H_5COCH_3$

CLIX → CH_3CONH_2
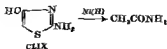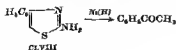
derivative.[42] If a hydroxyl group is interposed between the thiazole nitrogen and sulfur, and an amino group is attached in the 5 position, a rearrangement to a 2-hydroxyimidazole (e.g., CLX) takes place.[196] It

CLX
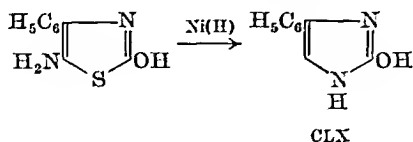
is claimed that the dibromothiazole CLXI on attempted desulfurization underwent only hydrogenolysis of halogen at the 2 position.[197] A careful
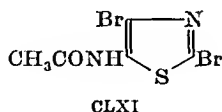
CLXI

study of the desulfurization reaction with 2-amino-4-phenylthiazole (CLXII) and several related compounds, employing W-6 (neutral) or W-7

CLXII

$$\xrightarrow{\text{Ni(H)}} C_6H_5COCH_3 + C_6H_5CH(NH_2)CH_3 + CH_3NH_2 + NH_3$$
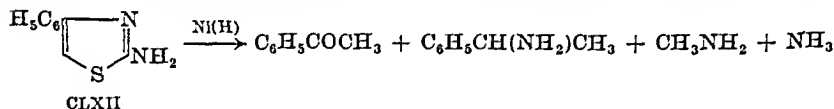
(alkaline) Raney nickel, has indicated that two competitive mechanisms are operative.[41, 161] For example, CLXII yielded both acetophenone and α-phenylethylamine.

Sulfoxides

Sulfoxides can be desulfurized successfully by Raney nickel. Instances in the literature are few, although only one unsuccessful attempt has been reported.[194] Diphenyl sulfoxide is hydrogenolyzed to benzene in good yield;[7, 198] n-propyl 2-hydroxy-2-phenylethyl sulfoxide is converted to the expected 1-phenylethanol along with some acetophenone.[199] The latter possibly arises from a nickel-catalyzed hydrogenation-dehydrogenation equilibrium.

The sulfoxide group can be removed selectively from the androstene and pregnene derivatives CLXIII and CLXIV,[101] leaving the double bonds and the carbonyl group intact. Of especial interest is the role that

[194] Cook, Heilbron, and Hunter, J. Chem. Soc., 1949, 1443.
[197] Prijs, Mengisen, Fallab, and Erlenmeyer, Helv. Chim. Acta, 35, 187 (1952).
[198] Mozingo, U.S. pat. 2,371,641, 1945 [C.A., 39, 4618 (1945)].
[199] Kharasch, Nudenburg, and Mantell, J. Org. Chem., 16, 524 (1951).

desulfurization played in the development of the structure CLXV for sulphoraphen, a natural product whose optical activity is due to the

$$CH_3SOCH=CHCH_2CH_2N=C=S \qquad (CH_3SO(CH_2)_4NH)_2CO$$
$$CLXV \qquad\qquad\qquad CLXVa$$

asymmetry of sulfur The urea CLXVa derived from this substance furnished N N'-di-n-butylurea on treatment with Raney nickel.[300]

Sulfones

Among the sporadic examples of sulfone desulfurization appearing in the literature are the transformations of diphenyl sulfone to benzene,[9,301] ethyl 1,1-diphenyl-3-(N,N-dimethylamino)-n-butyl sulfone to 1,1-diphenyl-3-dimethylaminobutane,[302] and thianaphthene sulfone dimer to ethylbenzene[303] Thianaphthene (CLXVI) gave an oil which has not been identified[303a] The monosaccharide derivative CLXVII is reported to undergo only olefinic saturation on attempted desulfurization[304] Tetrahydrothiapyran sulfone[76] also has been found to resist desulfurization.

CLXVI

[300] Schmid and Karrer, Helv Chim Acta, 31, 1017 (1948)
[301] Mozingo, U S pat 2,371,642, 1945[C A , 39, 4614 (1945)].
[302] Kleuk, Suter, and Archer, J Am Chem Soc , 70, 3845 (1948)
[303] Davies and James, J Chem Soc , 1955, 314
[303a] Davies, Porter, and Wilmshurst, J Chem Soc , 1957, 3366
[304] MacDonald and Fischer, J. Am Chem Soc , 74, 2087 (1952)

It has been claimed that hydrogenolysis of aryl sulfonic esters does not proceed by desulfurization but rather by formation of a nickel sulfonate.[208] Consequently the two preceding examples (CLXVIII and CLXIX) may simply involve hydrolysis and hydrogenolysis, respectively, without cleavage of the C—S bond.

Initial experiments have indicated that benzylsulfonamides respond particularly well to desulfurization, while *p*-toluenesulfonamides will probably require conditions more vigorous than those hitherto employed.[209]

Preliminary studies[213,216] involving the Raney nickel desulfurization of N-alkylsaccharin derivatives (e.g., CLXX) shows that hydrogenolysis to benzamides is easily accomplished in boiling ethanol. Since sodium
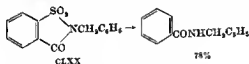
saccharin is readily alkylated by normally reactive halogen compounds,[211,212] desulfurization of the product, in principle, presents a mild procedure for conversion of alkyl halides to benzamides, amines, or, for example, amino acids.

Miscellaneous

Among the various examples of desulfurizations not belonging to one of the previously discussed types, but proceeding by simple desulfurization, are those falling in the thiocyanate,[213] 1,3,4-trithiacyclopentane,[214]

[208] G. R. Pettit and M. Madore Unpublished experiments
[209] Rice and Pettit, *J. Am. Chem. Soc.*, **76**, 302 (1954)
[213] Rice, Grogan, and Reid, *J. Am. Chem. Soc.*, **75**, 4304 (1953)
[214] Hann, Ruchtmyer, Diehl, and Hudson, *J. Am. Chem. Soc.*, **72**, 561 (1950)
[216] Campaigne and Reid, *J. Org. Chem.*, **12**, 807 (1947)

CLXXVI   33%
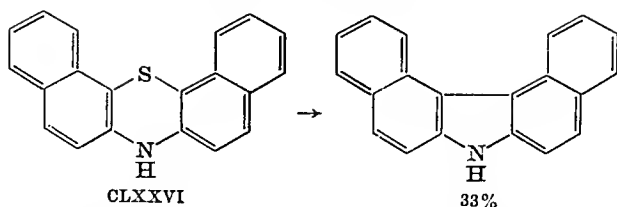
An early degradative technique applied to the antibiotic gliotoxin[227] was disruption of the disulfide linkage by the use of aluminum. Selective desulfurizations have been accomplished by zinc dust and hydrochloric acid as well as with iron powder in an alkaline medium: the trithioacid anhydride CLXXVII was transformed into the thiapyranone CLXXVIII

CLXXVII   CLXXVIII
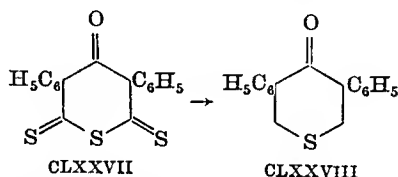
by zinc and acid,[228] and the 2-thiolthiazole CLXXIX was converted to the parent CLXXX by iron and alkali.[229] Warming a mixture of the thioether

CLXXIX   CLXXX
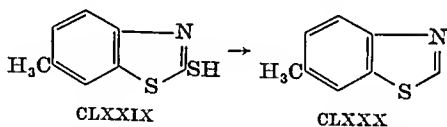
CLXXXI and zinc amalgam in a mixture of acetic and hydrochloric acid afforded a 91% yield of sulfur-free product. Reductive cleavage of a

$$CH_3CO(CH_2)_{12}COCH_3$$

CLXXXI
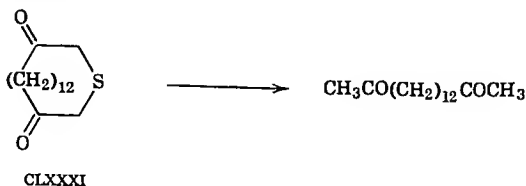
carbon-sulfur bond at position 2 or 3 in 1,4-naphthoquinones has been shown to occur in a boiling solution of stannous chloride in hydrochloric and acetic acids.[230]

[227] Johnson and Buchanan, *J. Am. Chem. Soc.*, **75**, 2103 (1953).
[228] Schönberg and Asker, *J. Chem. Soc.*, **1946**, 604.
[229] Blomquist and Diuguid, *J. Org. Chem.*, **12**, 718 (1947).
[230] Bruce and Thomson, *J. Chem. Soc.*, **1954**, 1428.

Selenium dioxide[231] has been used to replace a thiol group by hydroxyl Diphenylsilane has been shown to displace sulfur from certain aromatic systems (e.g., CLXXXII → CLXXXIII)[225]

CLXXXII   CLXXXIII
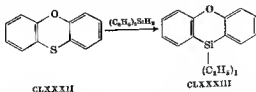
Oxidizing agents such as nitric acid[232] and hydrogen peroxide[233] have been used for the desulfurization of various heterocycles, including pyrimidine-2-thiols and thiazole-2-thiols, to the parent aromatic compounds.

Mercuric oxide has been used frequently for desulfurization of sugar mercaptals.[234,235] Mercuric sulfate,[236] lithium aluminum hydride,[225,237] copper, aluminum bromide, and organolithium compounds[228] have also been used to remove sulfur from various organic compounds.[228] Mercuric chloride has been found to regenerate ketones from hemithioketals (e.g.,
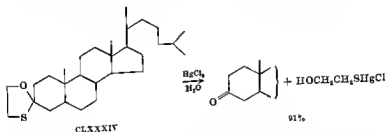
CLXXXIV   91%

CLXXXIV),[48] and a mixture of mercuric chloride and cadmium carbonate has been utilized in reversing thioketal (cf. CLXXXV) formation.[238,239] Thiophenes may be desulfurized by high-pressure hydrogenation in the presence of a tungsten-nickel sulfide catalyst.[240]

231 Monti and Franchis, *Gazz chim ital*, **71**, 764 (1951)
232 Jones, *J Am Chem Soc*, **71**, 383 (1949)
233 Buchman, Reims, and Sargent, *J Org Chem*, **6**, 764 (1941)
234 Zinner, Nimz, and Venner, *Chem Ber*, **4**, 425 (1958)
235 Whitehouse and Kent, *Tetrahedron*, **4**, 425 (1958)
236 Travagli, *Gazz chim ital*, **81**, 688 (1951) [*C A*, **46**, 6119 (1952)]
237 Ried and Müller, *Chem. Ber*, **88**, 479 (1955)
238 Cram and Cordon, *J Am Chem Soc*, **77**, 1810 (1955)
239 Sannié, Neuville, and Farnoux, *Bull soc chim France*, 1958, 635
240 Truitt, Hobst, and Sammons, *J Org Chem*, **22**, 1107 (1957)
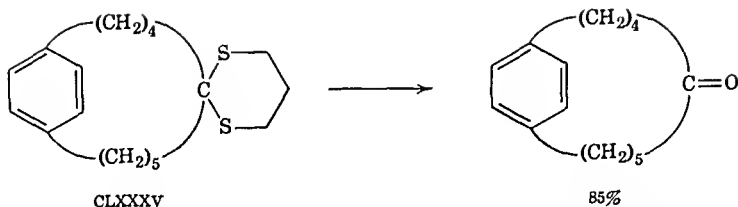
CLXXXV   85%

In two exceptional cases, desulfurization occurred in boiling piperidine (CLXXXVI → CLXXXVII)[241] and during the chromatography of certain azothiobenzenes on alumina.[242]

$$(CH_3SO_2)_2C(SCH_3)N{=}NC_6H_5 \rightarrow (CH_3SO_2)_2CHN{=}NC_6H_5$$
CLXXXVI   CLXXXVII
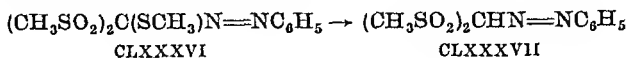
Triethyl phosphite has recently been introduced as a desulfurization reagent.[243-245] The stereoselective removal of sulfur from thiiranes (e.g., CLXXXVIII) is indicative of the potential value of this reagent.[246]

CLXXXVIII
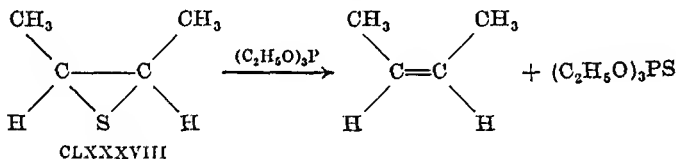
Another new desulfurization procedure involves the use of hydrazine and potassium hydroxide. The experimental procedure is reminiscent of the Wolff-Kishner reduction.[247] Wolff-Kishner reduction of the lanostane derivative CLXXXIX using vigorous conditions also resulted in desulfurization.[248] (Equation on p. 407.)

EXPERIMENTAL CONDITIONS

Raney Nickel. The Raney nickel catalysts have been designated W-1, W-2, W-3, W-4, W-5, W-6, and W-7 according to the procedure employed for their preparation.[249] Although the W-2 catalyst has been extensively used in desulfurization studies, the W-4 and W-7 catalysts appear to be

[241] Backer, Rec. trav. chim., 70, 892 (1951).
[242] Leandri and Rebora, Gazz. chim. ital., 87, 503 (1957).
[243] Hoffman, Ess, Simmons, and Hanzel, J. Am. Chem. Soc., 78, 6414 (1956).
[244] Davis, J. Org. Chem., 23, 1767 (1958).
[245] Schuetz and Jacobs, J. Org. Chem., 23, 1799 (1958).
[246] Neureiter and Bordwell, J. Am. Chem. Soc., 81, 578 (1959).
[247] Georgian, Harrison, and Gubisch, J. Am. Chem. Soc., 81, 5834 (1959).
[248] G. R. Pettit and W. J. Bowyer. Unpublished experiment.
[249] Billica and Adkins, Org. Syntheses Coll. Vol. 3, 176 (1955).

superior. Many examples of desulfurization have been reported in which the catalyst is generated *in situ* from nickel aluminum alloy.[33,49] Decomposition of Raney nickel alloy by strong base appears to constitute

CLXXXIX
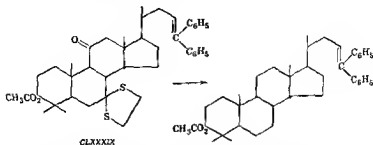
the most powerful desulfurizing conditions known, since only by means of this method can sulfonic acids be cleaved Unfortunately, many authors have not designated the particular type of nickel used, and, therefore, generalizations are difficult to formulate.

The different modifications of Raney nickel vary in the amount of hydrogen absorbed For example, if a temperature of 80° is attained in the preparation, the nickel contains 40–42 ml. of hydrogen per gram; *if the temperature is maintained at 50°,* 1 g. of the product contains about 120 ml. of hydrogen.[7] The quantity of hydrogen adsorbed becomes of considerable importance if the nickel is heated to 100–200° before the desulfurization. As Hauptmann has shown, partial desulfuration or desulfurization without hydrogenolysis is the usual course of reaction with "hydrogen-poor" or "hydrogen-free" nickel.[11,72] Badger[41] has described the preparation of a partially degassed W-7 Raney nickel catalyst Depending on conditions, the degassing process may be attended by an explosion hazard.[29]

In the usual case, the Raney nickel reagent is used in large excess by weight (at least ten times the weight of the sulfur compound) and is added as a suspension to a solution of the substance to be desulfurized. The quantity of nickel is best measured by weighing the nickel-aluminum alloy before preparing the nickel by treatment with base, or by measuring the nickel suspension by volume. For reproducible results, the nickel should be prepared on the order of hours or days before use; aging of the reagent for some weeks or months is attended by a noticeable deactivation.

Controlled hydrogenolysis of thiol esters and thioamides to produce aldehydes is ordinarily accomplished by subjecting a suspension of the

29 Snase, *J Chem Soc.* 1958, 3046

desired amount of nickel to the action of boiling acetone for a short time (usually about an hour or two) before adding the substance to be desulfurized.[149a] Apparently this treatment with acetone, a hydrogen acceptor, destroys most of the active centers on the nickel surface, producing a reagent more selective in its action. This treatment also seems to aid in preserving olefinic bonds[100] or carbonyl groups[75] which otherwise are reduced.

Occasionally workers have observed that strong adsorption of the desulfurized material on the nickel results in a poor recovery under the usual conditions of isolation. The difficulty has been surmounted by removing the product from the nickel with a suitable solvent in a Soxhlet extractor,[251] or by dissolving the nickel in a mineral acid.[163, 252]

Solvent. In general, solvent effects have seldom been noted. Neutral solvents such as water, methanol, ethanol, and dioxane are commonly used. Solvents which have been used less frequently include acetone,[23] benzene,[46, 253] butanol,[46, 38] decalin,[254] dimethylformamide,[98] ethylene glycol,[255] ethyl acetate,[28] methyl ethyl ketone,[46] mesitylene,[98] methyl Cellosolve,[83] Phillips 66, Soltrol 170,[254] tetrahydrofuran,[137] toluene,[183] and xylene.[35, 41] Occasionally, acetone[45] and low-boiling alcohols[65, 98] prove ineffective as solvents. Desulfurization of thiols can be carried out in aqueous ammonia,[71, 256] while certain acids can be reduced conveniently in aqueous potassium carbonate,[257] sodium carbonate,[163, 180] sodium bicarbonate,[258] or sodium hydroxide.[170, 259, 260]

Because of explosion hazard, dioxane *must not* be used with Raney nickel above 210°.[261] Pyridine has been found to yield 2,2′-dipyridyl when employed as a solvent with Raney nickel,[250,261a,262] while alcohols, ethanol in particular, may lead to N-alkylated products during desulfurization of amines.[18, 20, 21] An example of base-catalyzed C-alkylation by alcohols has recently been reported during desulfurization.[22]

The reaction mixture may be stirred, but this is usually not necessary if it is boiled under reflux. However, reactions employing large amounts of nickel (>25–50 g.) should be stirred.

[251] Modest and Szmuszkovicz, *J. Am. Chem. Soc.*, **72**, 577 (1950).
[252] Bernstein and Dorfmann, *J. Am. Chem. Soc.*, **68**, 1152 (1946).
[253] Berson and Jones, *J. Am. Chem. Soc.*, **78**, 6045 (1956).
[254] Grundmann and Kober, *J. Org. Chem.*, **21**, 641 (1956).
[255] Banfield, Davies, Gamble, and Middleton, *J. Chem. Soc.*, **1956**, 4791.
[256] Falco and Hitchings, *J. Am. Chem. Soc.*, **78**, 3143 (1956).
[257] Pettersson, *Arkiv Kemi*, **7**, No. 5, 39 (1954) [*C.A.*, **49**, 6219 (1955)].
[258] Sicé, *J. Am. Chem. Soc.*, **75**, 3697 (1953).
[259] Hansen, *Acta Chem. Scand.*, **8**, 695 (1954).
[260] Gundermann and Thomas, *Chem. Ber.*, **91**, 1330 (1958).
[261] Mozingo, *Org. Syntheses Coll. Vol.* **3**, 181 (1955).
[261a] Badger and Sasse, *J. Chem. Soc.*, **1956**, 616.
[262] Badger, Jackson, and Sasse, *J. Chem. Soc.*, **1960**, 4438.

Time and Temperature. It is very likely that the conditions used in many reported desulfurizations, viz., heating for several hours in a suitable solvent, are more vigorous than necessary. The mild conditions often sufficient for complete removal of sulfur are shown by the hydrogenolysis of a thiol ester to a primary alcohol, which can be accomplished quantitatively with W-4 nickel at room temperature in a few minutes;[154] and by the desulfurization of the thioketal CXC which proceeds in 90%

CXC
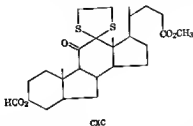
yield by heating in boiling methanol for 1 hour, and in 86% yield by shaking at room temperature for 15 minutes in the same solvent[263]

EXPERIMENTAL PROCEDURES

Degassed Raney Nickel Catalyst.[11] Raney nickel (53 g.) was transferred with benzene to a Carius tube and the solvent was evaporated under reduced pressure, while the nickel was held in place by means of a magnet. The dry nickel was degassed by heating for 2 hours at 200° and 2 mm.

4-Hydroxy-6-methyl-7-phenylpyrido(2,3-d)pyrimidine.[11a] Six grams of 2-mercapto-4-hydroxy-6-methyl-7-phenyl-pyrido(2,3-d)pyrimidine, m.p. 240–242°, was added to 1.8 L. of 95% ethanol and 150 ml. of concentrated aqueous ammonia. After the addition of approximately 18–20 g. of Raney nickel catalyst, the reaction mixture was heated under reflux for 6 hours on a steam bath. The catalyst was then removed by filtration and extracted with 300 ml. of boiling 95% ethanol. The combined filtrates were evaporated under reduced pressure on a steam bath until the volume was about 100 ml. The hot solution was adjusted to pH 5 with dilute acetic acid and allowed to cool. The crude yield of white needles was 4.4 g., m.p. 245–248°. Recrystallization from ethanol-water raised the melting point to 248–250°

3,5-Androstadien-17β-ol from the 3-Benzylthio Enol Ether of Testosterone.[190] A suspension of 30 g. of Raney nickel in 150 ml. of acetone was heated under reflux for 1 hour, 3.0 g. of the 3-benzylthio enol

190 S. Archer, Private communication.

Desulfurization of Spiro-(5-diphenylmethyl-1,3-oxathiolane-2,3'-cholestane).[4] Twenty grams of W-2 Raney nickel catalyst, 3 days old, was refluxed with stirring for 1 hour with 250 ml of methyl ethyl ketone, 2 0 g. of the hemithioketal isomer A (m.p 193–194°) was added and refluxing was continued with stirring for 24 hours (When the reaction was carried out in acetone solution, up to 80% of the hemithioketal was recovered)

The catalyst was separated on a filter, the solvent was removed, and the residue was chromatographed in 36 fractions over 30 g. of Merck acid-washed alumina. The first 25 fractions, eluted with petroleum ether, furnished 975 mg. (78%) of cholestan-3-one, m p 126–127°, while from the petroleum ether-benzene (1:1) eluates 20 mg. (2%) of cholestan-3β-ol, m p. 138–139°, was obtained. The last 6 fractions, eluted with benzene, were combined and treated in pyridine solution with 3,5-dinitrobenzoyl chloride in the usual fashion. Crystallization from hexane gave 676 mg (52%) of the 3,5-dinitrobenzoate of (+)1,1-diphenylpropan-2-ol as needles, m p, 154.5–155°, $[\alpha]_D^{25}$ −46 1° (CHCl₃)

Desulfurization of 1 0 g of the hemithioketal isomer C (m p. 152–153°), under precisely the same conditions, yielded 80% of cholestan-3-one and 57% of the 3,5-dinitrobenzoate of (−)1,1-diphenylpropan-2-ol, m.p 154.5–155°, $[\alpha]_D^{25}$ +44° (e = 1.7%, chloroform) Admixture with the above antipode lowered the melting point to 129–130°, which corresponds to the melting point of the racemic derivative which had been prepared independently

Desulfurization of γ-2-Thienylbutyric Acid.[16] The W-7 Rancy nickel catalyst from 125 g of alloy was added in one portion to 300 ml. of an aqueous solution of 20 g of γ-2-thienylbutyric acid in dilute sodium carbonate solution After 2 hours' stirring at 90–95° in an open beaker, the volume was 190 ml The mixture was added slowly to excess hydrochloric acid (condenser), and the resulting solution was continuously extracted with ether Distillation of the product gave (a) 11 5 g. of n-octanoic acid, b.p 165–170°/22 mm (p-bromophenacyl ester, m p 67°), (b) 3 g of γ-2-thienylbutyric acid, b p. 127–130°/0 6 mm (p-bromophenacyl ester, m p. 56 5–57 5°), and (c) 1 g. of residue. The residue was taken up in aqueous sodium carbonate, treated with charcoal, reprecipitated, recrystallized from ether, sublimed at at 200°/23 mm , and re-crystallized from concentrated nitric acid This furnished 0.05 g. of hexadecane-1,16-dioic acid as plates. m p. 123–124°.

Hydrogenolysis of 5-t-Butyl-2-thenoic Acid.[17a] To a well-stirred solution of 12 g of the thenoic acid in 100 ml of 10% aqueous sodium hydroxide heated at 90°, 100 g. of Raney nickel was added in small portions (with a few drops of isoamyl alcohol to prevent excessive frothing).

The mixture was then heated for 2 hours, filtered while hot, and the cooled filtrate was acidified with hydrochloric acid. The product was extracted with ether and purified by vacuum distillation. The 6,6-dimethylheptanoic acid, thus obtained in 70% yield, was a pale yellow oil with an unpleasant rancid smell, b.p. 143°/17 mm., n_D^{22} 1.4375.

Desulfurization of N-Benzylsaccharin.[210] A mixture of 1 g. of N-benzylsaccharin, 100 ml. of ethanol, and 15 ml. of W-4 Raney nickel (10 weeks old) was heated at reflux, with stirring, over a 13-hour period. The reaction mixture was filtered through a layer of Celite and the collected catalyst was washed with hot ethanol. After removal of the solvent under reduced pressure the crystalline residue was recrystallized from ethanol. The yield of colorless crystals, m.p. 96–99°, was 0.6 g. (78%). Three recrystallizations from ethanol gave pure benzylbenzamide, m.p. 104.0–104.5°.

TABULAR SURVEY

Unless otherwise noted, desulfurization of each of the indicated structures involves *only* replacement of sulfur by hydrogen. Compounds which contain more than one type of sulfur group will generally be found in the first table that would ordinarily describe one of the sulfur units. For example, a mercaptothiazole would be found among the thiols (Table I) instead of among the thiazoles. Location within each table is *usually* determined by whether the compound is aliphatic, aromatic, heterocyclic, carbohydrate, steroid, or a substance related to the steroids. In general, the entries are arranged by increasing carbon content, number of and size of rings, and in the order of increasing numbers of hetero atoms.

In most cases, compounds of the same basic structure are listed under a general formula, e.g.,
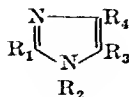
In the individual entries, the substituents only are listed so that any R group not named is hydrogen.

Yields given in these tables represent products obtained in reasonably high purity as evident from melting point or boiling point data; in most cases, yields of crude products or products of questionable purity have been omitted.

The literature available through February 1960 has been reviewed, and a number of more recent articles have been included.

TABLE I

RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
$HSCH_2CO_2H$		—	1
$HSCH_2CH_2SH$		—	1
$HSCH_2CH(OH)CH_2SH$		—	59, 265
$HSCH_2CH(SH)CH_2OH$		—	59, 265
$HSCH_2(CHOH)_4CH_2SH$ (1,6-dithiodulcitol)		—	60
$CH_3OCH_2CH_2SH(CH_2)_2H_2$		—	266
$(C_6H_5)_2C(OH)CH(SH)CO_2H_5$		—	275
$(CH_3)_3CH_2CO_2H$		—	63
$CH_3(CH_2)_4CH_2SH$		—	59
	CH_3SH / CH_3SH	—	207
		—	59
		—	56
C_6H_5SH	Biphenyl	23†	56
		—	11

* Products resulting from replacement of sulfur by hydrogen are not shown.

† Degassed Raney nickel was used.
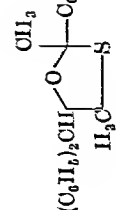
Note: References 265 to 490 are on pp. 525–529.

TABLE 1—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
2,6-(HO)₂C₆H₃SH		—	268
o-HO₂CC₆H₄SH		—	269
C₆H₅CH₂SH		—	269
p-CH₃C₆H₄SH		80	269
o-CH₃C₆H₄CH₂SH		—	270
C₆H₅NHCOCH₂SH		—	1
C₆H₅CH=C(SH)CO₂H		—	1
C₆H₅CH(SH)CH(NH₂)CO₂H·HCl		40	271
C₆H₅COC(CH₃)₂CONHCH₂CH₂SH	C₆H₅CHCHC(CH₃)₂CONHCH₂CH₃	—	25
(C₆H₅)₂C(SH)CO₂H		—	272
C₆H₅CH(SH)CH(OH)C₆H₆		—	45
(C₆H₅)₂CHCH(OH)CH₂SH	(a) C₆H₅CH₂CH₂CHOHC₄H₆, C₆H₅CH₂CH₂CH₂C₄H₆, and C₆H₅CH₂CH₂COC₄H₆	—	45
	(b) C₄H₄CH₂CH₂CH₂C₄H₆	55, —	45, 273
	(C₄H₆)₂CHCH₂CH₂OH	24, —	45, 273
	(C₆H₆)₂CHCOOH₃	Quant.	9, 50
(C₆H₅)₂CHCH(OH)CH₂SH	2-Methylanthraquinone, bis(2-anthraquinonylmethyl) sulfide, 2-hydroxyanthraquinone, and 2-anthraquinone-carboxylic acid	—	274
2-C₁₀H₇SH			
2-(Mercaptomethyl)anthraquinone			
(CH₃)₂C(SH)CHCO₂CH₃	NHCOCH(CH₂OH)NHCOCH₂C₆H₆	81	61
NHCOCH(CH₂OH)NHCOCH₂C₆H₆			

(structure)

$$N{-}{\parallel}{-}R_4$$
$$R_1{-}N{-}R_2$$
$$R_3$$

$R_1 = R_3 = SH$ CH_2CH_2OH $R_4 = CH_3CH(CO_2CH_2)CH_2NHCOC_2H_5$

$R_1 = SH, R_3 = CH=C\cdot CO_2CH_2NHCOC_2H_5$ —   64

$R_1 = SH, R_2 = C_2H_5$ —   276

$R_1 = SH, R_2 = CO_2C_2H_5$ 42   277

$R_1 = OH, R_2 = CO_2C_2H_5, R_3 = SH$ 31   278

$R_1 = SH, R_3 = NHCOCH_3$ —   279

$R_1 = SH, R_2 = NHCO_2C_2H_5$ 59   196

$R_1 = SH, R_3 = NHCO_2C_2H_5, R_4 = CH_3$ 65   280

$R_1 = SH, R_3 = NHCO_2C_2H_5, R_4 = C_2H_5$ 65   281

$R_1 = SH, R_2 = (CH_2OH)_2CH_2OH$ —   281

$R_1 = SH, R_2 = CH(OH)CH(SH)(CH_3)$ —   282

$R_1 = R_3 = CH_2, R_4 = NH_2$ —   62

$R_1 = R_3 = CH_2, R_4 = CO_2C_2H_5$ —   283

$R_1 = SH, R_4 = CH_2, R_2 = CH_3, R_3 = CO_2C_2H_5$ —   283

$R_1 = SH, R_4 = CH_2, R_2 = CH_3, R_3 = CONH_2$ —   283

R_2N—R_3
EB⟩N—X

$R_1 = C_2H_5$ 73   68

$R_1 = p\text{-}CH_3OC_6H_4$ 59   68

$R_1 = p\text{-}ClC_6H_4$ 55   68

$R_2 = NHN=CHC_6H_5$ 47   284

$R_2 = NH_4, R_3 = C_2H_5$ 41   284a

$R_1 = R_2 = NH_4$ 33   284

$R_1 = C_2H_5CH=N, R_3 = NHN=CHC_6H_5$ 26   284

Note: References 262 to 490 are on pp. 525-529.

‡ Acetone was used as the solvent.
† Ethanol was used as the solvent.

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE I—Continued
RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
(thiazole) R_2—N, R_1—S—SH	CH_3CHO $R_2 = C_6H_5 + C_6H_5COCH_3$		
$R_2 = OH$		72	43
$R_2 = C_6H_5$		16, 48	43
$R_1 = NH_2$, $R_2 = C_6H_5$		—	278
$R_1 = NHCOCH_3$, $R_2 = C_6H_5$		—	278
$R_1 = CH_2CH_2OH$, $R_2 = CH_3$		—	285
(pyrimidine) R_3, R_2, R_1, N, N, SH			
$R_1 \ldots , R_2 = H$		—	65
$R_1 = R_3 = CH_3$		54	65
$R_1 = CH_3(CH_2)_4NH$		68	280
(piperidine) R_1, N			
$R_1 =$		65	280
$R_3 = NH_2$		20, 61	280a, 287
$R_1 = NH_2$, $R_3 = OH$		18	142
$R_1 = R_3 = NH_2$		24, 85	280a, 287
$R_2 = R_3 = NH_2$		—, 00	288, 72
$R_1 = OH$		82	287

$R_1 = R_2 = R_3 = NH_2$

$R_1 = R_3 = NH_2,\ R_2 = OH$	78, 89
$R_1 = R_3 = NH_2,\ R_2 = NO$	47
$R_1 = R_2 = NH_2,\ R_3 = NH_2$	78
$R_1 = R_2 = NH_2$	17

72, 66, 73
50
60
65

67

68
69

288a
288d

289

58
65

$R = C_6H_5CH_2$
$R = p\text{-}ClC_6H_4CH_2$

$R_2 = H$
$R_3 = NH_2$

Note: References 265 to 450 are on pp. 525–529.

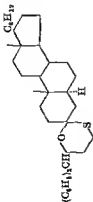* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE I—*Continued*
RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
R_1 = SH		41–48	71, 200
R_1 = R_2 = SH		35	71
R_1 = SH, R_3 = CH_3		—	291
R = H		—	256
R = OH_3		—	292
		53	293

	References
—	294
—	294
—	294
—	294
—	294
—	294
—	294
30	295
90	296
57	293
57	296
—	297

$R_1 = CH_3, R_3 = OH$
$R_1 = C_2H_5, R_3 = OH$
$R_1 = i\text{-}C_3H_7, R_3 = OH$
$R_1 = p\text{-}ClC_6H_4, R_3 = OH$
$R_1 = CH_3, R_3 = NH_2$
$R_1 = C_2H_5, R_3 = NH_2$
$R_1 = CH_2CH(CH_3)_2, R_3 = NH_2$

$R = H$
$R = C_2H_5$
$R = CH_2C_6H_5$

Note: References 285 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE I—Continued

RANEY NICKEL DESULFURIZATION OF THIOLS

Thiol	Product*	Yield, %	References
(quinoxaline with SH, NH(CH₂)₃N-piperidine, Cl)		—	208
(pteridine with NH₂, HS, SH)		—	298a
$R_1 = R_3 = CH_3$		83	71a
$R_2 = R_3 = CH_3$		09	71a
$R_2 = CH_3, R_3 = C_2H_5$		80	71a
$R_3 = CH_3CH(CH_3)CH_2$		06	71a
$R_2 = C_2H_5, R_3 = n\text{-}C_3H_7$		80	71a
$R_2 = CH_3, R_3 = n\text{-}C_4H_9$		76	71a
$R_3 = C_6H_5$		44	71a
$R_3 = p\text{-}CH_3C_6H_4$		74	71a
$R_3 = p\text{-}ClC_6H_4$		01	71a
$R_2 = CH_3, R_3 = C_6H_5$		84	71a
$R_2 = C_2H_5, R_3 = C_6H_5$		58	71a
$R_2 = C_6H_5, R_3 = C_6H_5CH_2$		08	71a

	Yield	References
(benzothiazole structures) + $[2\text{-}H_2NC_6H_4]_2S_3$	55	41, 299, 43
$C_6H_5NHCH_3$, $C_6H_5NH_2$	7,‖ 6†	41
	10,‖ —†	41, 43
	—‖ 33†	41
2-Methyl-5-mercaptothiazolo-5,4-pyrimidine	47,‖ 22†	41, 43
	17,‖ 1†	300
	—|	
(structure: CH_2SH, Cl_3CO_2, $COOCH_3$, $COOCH_3$)	70	301
2‡-Mercaptocholestan-3β-ol		
(a) Cholestan-3β-ol and cholestan-3-one‡	—|	45,‖ 45
(b) Cholestan-3-one‡	80	45
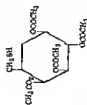
Note: References 265 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.
† Degassed Raney nickel was used.
‡ Acetone was used as the solvent.
§ Sodium hydroxide solution and W-5 Raney nickel were used
‖ Benzene was used as the solvent.
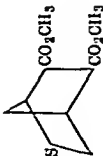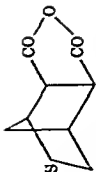
TABLE II

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
$n\text{-}C_4H_9SCH_3$		—	50
$(n\text{-}C_3H_7)_2S$		—	50
$[CH_3CH(CH_3)CH_2]_2S$		—	50
$CH_3S(CH_2)_3CO_2H$		95	7
$D(+)\text{Methionine}$	D(−)-α-Aminobutyric acid	17	104
$L(-)\text{Methionine}$	L(+)-α-Aminobutyric acid	—	85
$CH_3SCH\!=\!C(SCH_3)CO_2H$	$CH_3CH_2CO_2H$	80	200
$S(CH_2CH_2CH_2CO_2H)_2$		94	7
$[HO_2CCH(NH_2)CH_2CH_2SCH_2]_2$		—	304
$HOCH_2CH_2O(CH_2)_2SCH_2CH(NH_2)CO_2H$		—	300
$C_6H_5CH\!=\!CHCH_2SC_4H_9$		—	302
$HO_2CCH(NH_2)CH_2SCH(CH_3)CH(NH_2)CO_2H(?)$		—	303
$[CH_2CH_2CH_2OCO(CH_2)_2SCH_2]_2N$		—	305
$p\text{-}CH_3C_6H_4S$ (bicyclic, CO_2CH_3, CO_2CH_3)		70	253
$p\text{-}CH_3C_6H_4S$ (bicyclic anhydride, $CO\!-\!O\!-\!CO$)		38	253
cis-3-Methyl-3-benzylthiocyclohexyl β-naphthoate		80	307

trans-3-Methyl-3-benzylthiocyclohexyl β-naphthoate SC₂H₄	88	307
(structure) SO₂H	53	307
(structure)	—	308
(decalin) CH₃ ... OH	63	37
Petroleum thioethers		
CH₃SCH₂C₆H₅ OCH₂C₆H₅		309
p-CH₃C₆H₄SCH₃		7
p-CH₃C₆H₄SCH₂C₆H₅		11
p-CH₃C₆H₄CH₂CH₃	87	
(p-CH₃C₆H₄)₂	21	
	10	
	91	
o-HO·C₆H₄·SCH₂CO₂H		310
H₂NCH·CH(SO₂H)CO₂H (C₆H₅)₃	68, —	7, 66
(a)	75	11
(b)† (C₆H₅)₂ p-Terphenyl	6	

Note: References 205 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

† Degassed Raney nickel was used.

TABLE II—Continued

RANEY NICKEL DESULFURIZATION OF THIOETHERS

| Thioether	Product*	Yield, %	References
$(C_6H_5)_2S + 2,2'-(C_{10}H_7-)_2S$	Biphenyl	63	11
	2,2'-Binaphthyl	63	78
	2-Phenylnaphthalene	25	7
	Benzene†	7	7
$C_6H_5CH_2SC_6H_5$	$C_6H_5CH_2CH_2C_6H_5$†	—	78
$(C_6H_5CH_2)_2S$		85	311
$(p\text{-}CH_3OC_6H_4)_2S$	$(p\text{-}CH_3OC_6H_4)_2$†	87	312
$(p\text{-}CH_3OC_6H_4)_2S$		50	16
$C_6H_5CH(SC_6H_5)COONH_2$		68	16
$1,1'\text{-}(C_{10}H_7-)_2S$		89	209
$C_6H_5C(CH_3)(CO_2H)SC_6H_5$		11	98
$C_6H_5C(CH_3)(CONH_2)SC_6H_5$		85	75
$C_6H_5S(CO_2H){=}CHC_6H_4OH\text{-}p$	$HO_2CCH_2CH_2C_6H_4OH\text{-}p$	—	75
$C_6H_5COOH(C_6H_5)SCH_2CH_3$		—	75
$p\text{-}CH_3OC_6H_4COCH(C_6H_5)SCH_2CO_2H$		—	75
$C_6H_5COOH(C_6H_{10}CH_3\text{-}p)SCH_2CO_2H$		—	
$C_6H_5COOH(C_6H_5)SC(CH_3)_2CO_2H$		—	
$p\text{-}(CH_3)_2NC_6H_4COOH(C_6H_5)SCH_2CO_2H$		—	
$CH_3C(OC_6H_5)_2CH_2CH_2SCH_2CH_2(CH_2)_2CH_3$	$CH_3CH(NHCOC_6H_{11})CO_2H$	Quant.	313
$S(CH_2CH(NHCOC_6H_5)CO_2H)_2$	$C_6H_5OH_3$ and $[o\text{-}CH_3OC_6H_4CH(C_6H_5)]_2$	60	314
$o\text{-}CH_3OC_6H_4CH(C_6H_5)SCH_2C_6H_5$	$C_6H_5CONHCH_2C_6H_5$ and $(C_6H_5CH_2)_2$ (traces)	—	315
$o\text{-}C_6H_5CH_2SC_6H_4NONHCH_2C_6H_5$		—	13

$(C_6H_5)_3CS$ — R — (benzene ring structure)

		318
	60	316
	55	316
	54	316
	63	75
		317
	90	79
	—	
	50	79
	—	86, 87
	—	

R = H,
R = o-CH₃,
R = m-CH₃,
R = p-CH₃

$C_6H_5COOHC_6H_4SCH_2CONHC_6H_5$
$C_6H_4CHSCH_2CH_2$-$pN(COCH_3)C_6H_5$

$C_6H_5CH_2N(COCH_3)C_6H_5$
$C_6H_4CH_3$

Note: References 265 to 490 are on pp. 625–629.

* Products resulting from replacement of sulfur by hydrogen are not shown.

† Degassed Raney nickel was used.

TABLE II—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
naphthalene with CH$_2$SC$_2$H$_5$, OH		75	318
tricyclic, CO$_2$CH$_3$, SCH$_3$, CH$_3$O, CH$_3$O, CH$_3$O		75	319
(CH$_3$)$_2$, C$_6$H$_5$, —SCH$_3$, —NC$_6$H$_5$, O= (β-lactam)		30	320
=CHSC$_6$H$_4$OH$_3$-p oxindole (O=, N–H)	oxindole CH$_3$ (O=, N–H)	—	81
=CHSC$_6$H$_4$OH$_3$-p, =CHCO$_2$CH$_2$CH$_3$ indole (N–H)	indole CH$_3$, CH$_2$CO$_2$H (N–H)	—	81

C$_6$H$_5$OH$_2$CH$_2$C	—	321
CH$_2$SCH$_2$CH$_3$	70	7
H$_3$C ... CH$_2$SC$_2$H$_5$	56	318
R$_1$ ... CH$_2$S ... NR$_2$	45	136
	90	136
	55	136
	61	136

R$_1$ = R$_2$ = C$_2$H$_5$
R$_1$ = C$_2$H$_5$, R$_2$ = CH$_3$
R$_1$ = C$_2$H$_5$, R$_2$ = CH$_3$
R$_1$ = R$_2$ = cyclopentyl

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE II—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
$O=$ ...NR$_1$, (C$_6$H$_5$)$_2$, N=, SR$_2$	$O=$ ...NR$_1$ (C$_6$H$_5$)$_2$, N= (I) $+$ $O=$ ...NR$_1$, (C$_6$H$_5$)$_2$, N—H (II)		
R$_1$ = R$_2$ = H	(a) II	79	139
	(b)‡ I	75	139
	Mixture of I and II	—	139
R$_2$ = CH$_3$	(a) 3:1 mixture of I and II	—	139
R$_1$ = R$_2$ = CH$_3$	(b)‡ I	84	139
R$_2$ = CH$_2$C$_6$H$_5$	(a) Mixture of I and II containing 25% of I	—	139
	(b)‡ I	85	139
R$_2$ =	$O=$ ...NH, (C$_6$H$_5$)$_2$, N=	Quant.	141
$\left(\text{—CH}_2\text{SCH}_2\text{CH}_2\text{—NH} \quad \begin{array}{c} \text{C}_6\text{H}_5 \\ \text{O}= \quad \text{N} \quad =\text{O} \end{array}\right)_2$		75	322
indol-CH$_2$SCH$_2$(CH$_2$)$_2$CH$_3$ (N—H)		62	318

80	—
48	}
290 290 296	28 51 59
84	58

$R_1 = CH_3$
$R_1 = C_6H_5, R_1 = CH_3$
$R_1 = C_2H_5, R_1 = C_2H_5/CH_3$

• Products resulting from replacement of sulfur by hydrogen are not shown.

‡ Sodium chloride was added to the reaction mixture.

TABLE II—*Continued*
RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
(structure: pyrimidinone with CH₃, N, SR, N-H, O) $R = CH_3$ $R = C_2H_5$		— —	323 323
(structure with SCH_2CH_2-) $R =$		—	323
(structure with $SOCH_2CH_2OH-$) $R =$		—	323
(pyrazine structure R_4, R_3, R_2, R_1) $R_1 = SOH, R_3 = Br$	(pyrazine)	—	65

75		325
		60
		289
		50
48		321
60		83
Low		12
10		254
22		254
81		327
		327
		325

$R_1 = SCH_3, R_2 = NO_2$

$R_1 = SCH_3, R_3 = NH_2, R_4 = OH$
$R_1 = SCH_2CO_2H, R_3 = p\text{-}CH_3OC_6H_4NH$
$R_1 = SCH_3, R_3 = OH, R_4 = C_6H_5CONH$
$R_1 = SCH_2C_6H_5, R_3 = C_6H_5CH_2SCH_2, R_4 = OH$
$R_1 = SCH_3, R_3 = NH_2, R_4 = NHCHO, R_4 = N(CH_3)_2$

$R_1 = SCH_3, R_2 = NH_2, R_3 = N=NC_6H_4Cl, R_4 = CH_3CO_2$
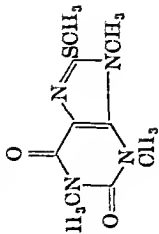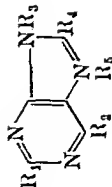
$R_1 = SCH_3$
$R_2 = CH_3, R_3 = R_4 = SCH_3$
$R_1 = C_6H_5, R_3 = SCH_3$
$R_2 = R_3 = C_6H_5, R_4 = SCH_3$

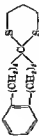Note: References 205 to 490 are on pp. 525–529.
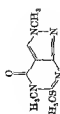
* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE II—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
		25	293
	R_1 = CH₃S, R_2 = NH₂, R_3 = CH₃	—	328
	R_1 = SCH₃, R_2 = N(CH₃)₂, R_3 = CH₃, R_4 = SCH₃	72	331
	R_1 = SCH₃, R_2 = N(CH₃)₂, R_3 = C₂H₅, R_4 = SCH₃	74	331
	R_1 = SCH₃, R_2 = N(CH₃)₂, R_4 = SCH₂C₆H₅	0	83
	R_1 = SCH₃, R_2 = N(CH₃)₂	43	83
	R_1 = R_4 = SCH₃, R_2 = N(CH₃)₂	10	83
	R_1 = R_4 = SCH₃, R_2 = N(CH₃)₂, R_5 = CH₃	50	331
	R_1 = R_4 = SCH₃, R_2 = N(CH₃)₂, R_5 = C₂H₅	42	331
	R_1 = CH₃S, R_2 = NH₂, R_3 = triacetyl-D-xylopyranosido-	—	328
	R_1 = CH₃S, R_2 = NH₂, R_3 = tetraacetyl-D-glucopyranosido-	—	320
	R_1 = CH₃S, R_2 = NH₂, R_3 = tetraacetyl-D-mannopyranosido-	—	330
	R_1 = CH₃S, R_2 = NH₂, R_3 = β-D-ribofuranosyl-	50, —	92, 93
	R_1 = SCH₃, R_2 = NH₂, R_3 = triacetyl-5-benzyl-D-ribofuranosyl	—	93
	6-Acetamido-9-[3',5'-di-0-acetyl-2'-deoxy-2'-(ethylthio)-β-D-arabinofuranosyl]purine	—	332

	Fair	333
	72	334
	45	284a
	62	90
	27-29	98, 99

$C_6H_5CONH_2$

$C_6H_5CH_2CONH_2$ CHCl₂H / CHCO₂H

$C_2H_4CH_2CONHCHBrCl_3$
    CONHCH(CH₂)₃CO₂H
    +
$C_3H_4CH_2CONHCHBrCl_3$
    CONHCH₂OH(CH₃)₃
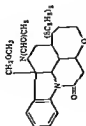
Note: References 205 to 490 are on pp. 525-529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE II—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
$O=$ NH $(CH_2)_5CO_2R$, S ring R = H R = CH_3		— —	40 40
$C_6H_5CH_2CONHCH$— S $(CH_3)_2$, HN CO_2H R = CO_2CH_3 R = H		— —	39 335
C_6H_5, $(CH_3)_2$, S, N, $O=$ structure		—	39, 336
C_6H_5CONH, S, N, CO_2H, $O=$ structure		—	337

R = H, R = CH₃	30	97
	35	97
Bacitracin A	—	338
C₆H₉CONH—(CH₂)₄CO₂CH₃ (Biotin methyl ester)	—	94
Biotin C₆H₉CONH—(CH₂)₄CO₂H	50–60	95
C₂H₅CH₂CO—N—(CH₂)₂—N—CO₂CH₃	—	95
		339

Note: References 205 to 400 are on pp. 525–539.
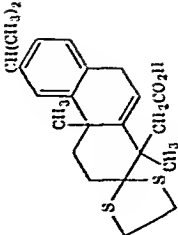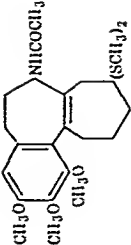
* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE II—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
(structure: fused ring bearing $COCH_3$, $(CH_3)_2$, N—H, C=O, S)		56	340
(structure: tetrahydrothiopyran, six-membered S ring)		—	56
	(structure: cyclopentane ring) + $n\text{-}C_5H_{12}$ and olefins	1	76
(structure: CH_3-substituted tetrahydrothiopyran-4-one, with =O, two CH_3, S)		—	340a
(structure: bicyclic fused thioether)		—	341

		—	341
	cis and trans	—	342
	cis and trans	—	342
	cis and trans	—	342
	CH_3 cis + trans +	Good	78
		1	78

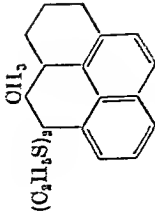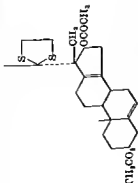*Note:* References 265 to 400 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE II—Continued

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
		72	99
	(a)§ C$_6$H$_5$CH$_2$CH$_2$CO$_2$H, C$_6$H$_5$CHOHCH$_2$CO$_2$H	—	99
	(b)‖ C$_6$H$_5$COCH$_3$, C$_6$H$_5$CHOHCH$_2$OCH$_2$CO$_2$H	—	99
	C$_6$H$_5$(CH$_2$)$_3$CO$_2$H	—	70
 (Ciba Scarlet G)	(a)§ (?)	—	99
	(b)‖ 1-Phenacyltetrahydroacenaphthene (?)	—	99
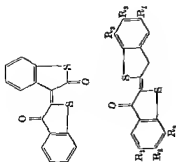
Structure	Products	Yield
	(a) $C_6H_5CHOHCH_2CHOHC_6H_5$ (?)	99
	(b)‖ $CH_3CH(OH)CH_2CH_2C_6H_5$ (?)	99
		—
		—
	(a) $C_6H_5(CH_2)_2C_6H_5$	70
	(b) $C_6H_5COCH_2CH_2COC_6H_5$	1
	$C_6H_5(CH_2)_4C_6H_5$	14
	$C_6H_5CO_2H$	5
	$p\text{-}C_2H_5C_6H_4CH_2C_6H_4CO_2C_2H_5\text{-}p$	59
	(a) $m\text{-}CH_3C_6H_3CHOHCH_2C_6H_4CH_3\text{-}m$	343
	(b) $3\text{-}Cl,5\text{-}CH_3C_6H_3COCH_2COC_6H_3Cl\text{-}3,CH_3\text{-}5,$	99
	$3\text{-}Cl,5\text{-}CH_3C_6H_3COCH_2COC_6H_3CH_3\text{-}3,$	99
	and $3\text{-}Cl,5\text{-}C_6H_3CH(OH)CH_2C_6H_3CH_2CH_3\text{-}3$	99
	(c) Undentified chlorine-free oil	—

$R_1, \ldots, R_3 = H$

$R_3 = C_2H_3O$
$R_2 = Cl, R_1 = CH_3$
(Durinden Red 33E)

Note: References 265 to 400 are on pp. 555–629.

TABLE II—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
 (Durindone Brown GS)	(a)§ $1\text{-}C_{10}H_7CO(CH_2)_2COC_{10}H_7\text{-}1$ and yellow liquid (b)‖ Colorless liquid.	— —	99 99
 Ciba Brown 2R¶	$1\text{-}C_{10}H_7CHOH(CH_2)_2CHOHC_{10}H_7\text{-}1$ $1\text{-}C_{10}H_7CO(CH_2)_2COC_{10}H_7\text{-}1$	Trace —	99
 (Mixture of isomers)		20, 30	344
		Fair	345

	Yield	Ref.
	94	346
	75	24
3-Trimethyl-4,6-benzylidene-β-methyl-d-glucoside	92	30
2-Thiomethyl-4,6-benzylidene-α-methyl-d-glucoside	57	347
4,6-Benzylidene-α-methyl 2-methylthio-2-deoxy-altroside	—	348
4,6-Benzylidene-α-methyl-2-thylthio-2-deoxyaltroside		
2-Deoxy-4,6-benzylidene-α-methyl-d-guloside		349
	1	350
	28	350

$R = 5'$-butyl-3'-deoxy-3'-thiobutyl-7-β-d-ribofuranosyl]
$R_F = 3'$-inoethyl-O,O-diacetyl-7-α-d-arabofuranosyl]
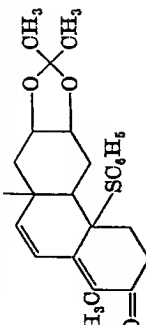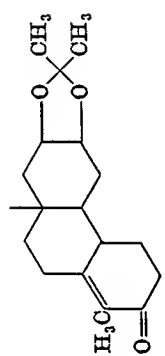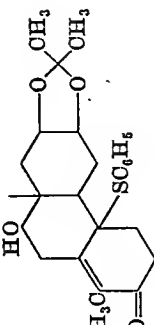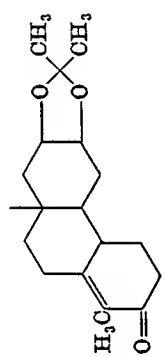
Note: References 205 to 490 are on pp. 525–529.

§ Aqueous sodium hydroxide was used in this experiment.

* Products resulting from replacement of sulfur by hydrogen are not shown.

|| Ethanol was used as the solvent.

TABLE II—Continued

RANEY NICKEL DESULFURIZATION OF THIOETHERS

Thioether	Product*	Yield, %	References
2-Thioethyl-D-glucose dimethyl acetal (or tetrabenzoyl derivative)	2-Thioethyl-D-glucose dimethyl acetal (or tetrabenzoyl derivative)	82	88
3-Thiomethyl-β-methylxylopyranoside		70–75	89
2-Acetamido-2-deoxy-α-D-glucopyranosylthioethane		—	351
2-Acetamido-2-deoxy-β-D-glucopyranosylthioethane		—	351
(steroid structure: H_3C, O, acetonide O–O, CH_3, CH_3, SC_6H_5)	(steroid structure: H_3C, O, acetonide O–O, CH_3, CH_3)	—	28
(steroid structure: H_3C, O, HO, acetonide O–O, CH_3, CH_3, SC_6H_5)		—	28
3-Benzyl thio enol ether of 4-androstene-3,17-dione	Androstan-17β-ol** and 3,5-androstadien-17-one	—	100
3-Benzyl thio enol ether of testosterone	(a) 3,5-Androstadien-17-β-ol** (b) Androstan-17-β-ol	87	100
3-β-Hydroxyethyl thio enol ether of testosterone	3,5-Androstadien-17-β-ol and androstan-17-β-ol	—	100
3-β-Hydroxyethyl thio enol ether of testosterone		83	100
3-Benzyl thio enol ether of 16-dehydroprogesterone		70	101

3-Benzyl thio enol ether of progesterone	69	101
21-Thiomethylpregnane-3α,20α-diol-11-one	—	352
21-Thiomethylpregnane-3α,20β-diacetoxy-11α-hydroxy-11-one	—	352
3β-Acetoxy-20-ethyl thio enol ether of 5-pregnen-20-one	82	353
3β-Acetoxy-18-thiobenzyl-5-pregnen-20-one	90	101
3-Benzyl thio enol ether of deoxycorticosterone 21-acetate	78	101
3-Thioethyl-5-cholesten-7-one 7-Cholestanol	55	103
Benzyl thio enol ether of cholestenone (a) 3,5-Cholestadiene**	88	100
(b) Cholestane		
3,3'-Thiodi-(5β-cholestane)	—	354
22β-3-(β-Hydroxyethylmercapto)spurosta-3,5,7-triene 22β-Spurosta-3,5,7-triene	—	102
+ 5,7-diene		
Benzyl thio enol ether of 4-norpirostan-3-one	78	101
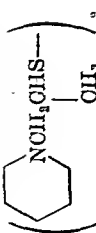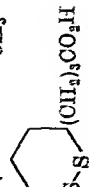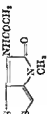
Note: References 205 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

** Raney nickel deactivated with acetone was used.

TABLE III

RANEY NICKEL DESULFURIZATION OF DISULFIDES

Disulfide	Product*	Yield, %	References
$(C_2H_5S)_2$		—	56
$(n\text{-}C_4H_9S)_2$		—	56
$(SCH_2CO_2H)_2$		—	1
$[SCH_2CH(NH_2)CO_2H]_2$		—	104
(cyclic: NCH_2CHS—, CH_3)		25	355
(cyclic: S–S ring, $(CH_2)_3CO_2H$)		—	356, 357
$(C_6H_5S)_2$	(a) Benzene	—	200
	(b)† Biphenyl	78	11
	p-Terphenyl	Trace	
	(c)‡ $(C_6H_5)_2S$	87	11
	(d)§ Biphenyl	54, —	11, 113
	Benzene	18	
	p-Terphenyl	0.2	
$(m\text{-}CH_3C_6H_4S)_2$	(a)‡ $(m\text{-}CH_3C_6H_4)_2S$	75	11
	(b)‖ $(m\text{-}CH_3C_6H_4)_2$	58	
$(p\text{-}CH_3OC_6H_4S)_2$ (degassed nickel)		—	78
$(C_6H_5CH_2S)_2$		—	56
$[SCH_2CH(NHCOC_6H_5)CO_2H]_2$		81	7
$(2\text{-}C_{10}H_7S)_2$†	$(2\text{-}C_{10}H_7)_2$	08–81	11
	Naphthalene	8–19	

$(C_2H_5S)_2 + (2-C_{10}H_7S)_2$ †	$(2-C_{10}H_7)_2$ $2-C_{10}H_7H$, Biphenyl Naphthalene Benzene	32 23 9 — — —	31
Bis-(2-anthraquinonylmethyl) disulfide	2-Methylanthraquinone, 2-hydroxyanthraquinone, and anthraquinone-2-carboxylic acid	—	274
		70	358
		—	299
Dibenzothiazole disulfide (a) Benzothiazole (b) $C_6H_5NHCH_3$ and $C_6H_5NH_2$		14	359
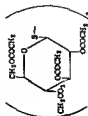
Note: References 285 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.
† Degassed (200°) Raney nickel was used without solvent at 220°.
‡ Degassed (200°) Raney nickel was used with benzene at 140°.
§ Degassed (200°) Raney nickel was used with benzene at 160°.
‖ Degassed (200°) Raney nickel was used with benzene at 180°.
¶ Degassed (200°) Raney nickel was used with benzene at 220°.
" The experiment was run in basic solution.
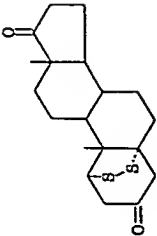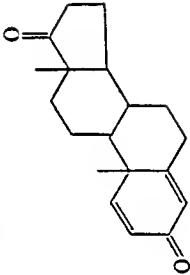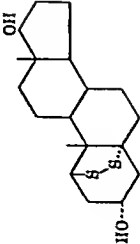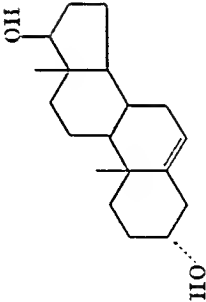
TABLE III—Continued
RANEY NICKEL DESULFURIZATION OF DISULFIDES

Disulfide	Product*	Yield, %	References
		—	300
		20	300

Note: References 265 to 400 are on pp. 525–259.

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE IV

RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS
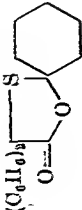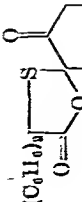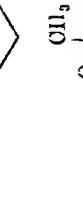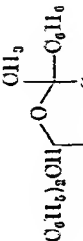
Hemithioketal	Product[*]	Yield, %	Reference
	HOC₂H₄OH	—	361
	Cyclohexane-1,2-diol and 2-hydroxycyclohexanone[†]	—	44
	2-Ethoxycyclohexanone, 2-ethoxycyclohexanol, 2-hydroxycyclohexanone, and cyclobutane-1,2-dione[†]	—	44
	2-Ethyl-2-hydroxycyclohexanone[†]	—	44
	Cyclohexanone $C_6H_5CH_2CHOHC_2H_5$ $C_6H_5CH_2COC_2H_5$ $C_6H_5CH=CHC_2H_5$[†]	70 42 — —	45

Note. References 205 to 490 are on pp. 495-528.
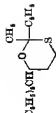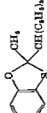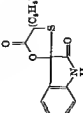
[*] Products resulting from replacement of sulfur by hydrogen are not shown.

[†] Acetone was used as the solvent.

TABLE IV—Continued

RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS

Hemithioketal	Product*	Yield, %	Reference
$(C_6H_5)_2$ O= structure with S, C_6H_5	(a)‡ $(C_6H_5)_2CHCO_2H$ and $(C_6H_5)_3CHCO_2C_2H_5$ (b)† $(C_6H_5)_2CHCO_2H$ and C_6H_5CHO	— —	272
$(C_6H_5)_2$ O= structure with S, cyclohexyl	(a)‡ $(C_6H_5)_3CHCO_2C_2H_5$ and $(C_6H_5)_2CHCH_2OH$ (b)† $(C_6H_5)_3CHCO_2H$ and cyclohexanone (c)§ $(C_6H_5)_2CHCH_2OH$ and cyclohexanone	— — —	272
$(C_6H_5)_2$ O= structure with S, cyclohexanone	$(C_6H_5)_2CHCO_2H$ and cyclohexanediol‡	—	272
$(C_6H_5)_2CH$ H_3C structure with $C_6H_4OCH_3$-p?, O, S, CH_3	(a)§ $(C_6H_5)_2CHCH_2OH_3$ p-$CH_3OC_6H_4COCH_3$ (b)† $(C_6H_5)_2CHCH(CH_3)OCH(CH_3)C_6H_4OCH_3$-p? p-$CH_3OC_6H_4COCH_3$ $(C_6H_5)_2CHCH(OH)CH_3$	81 72 42 38 27	46
$(C_6H_5)_2CH$ structure with C_6H_5, O, S, CH_3	(a)‖ $C_6H_5COCH_3$ $(C_6H_5)_2CHCHOHCH_3$ $(C_6H_5)_2CHCH_2OH_3$ $(C_6H_5)_2CHCH(CH_3)OCH(CH_3)C_6H_5$ $(C_6H_5)_2C=CHCH_3$ (b)§ $(C_6H_5)_2C=CHCH_3$ $(C_6H_5)_2CHCH(OH)CH_3$	47–71 37–62 10–32 0–32 0–1 90–96 2–5	46

Structure	Products*	Yields	Refs.
(C₂H₅)₂CH— ring with CH₃ and S	(a)‖ $C_3H_7COCH_3$	72–81	46
	$(C_2H_5)_2CHCH(OH)CH_2CH_3$	56–59	
	$(C_2H_5)_2CHCHCH_2CH_2OCHCH_3)C_2H_5$	13–20	
	(b)§ $C_3H_7COCH_3$	45–57	
	$(C_2H_5)_2CHCHCH_2CH_2OCH_3$	19–57	
	$(C_2H_5)_2CHCHCH_2CH_2OCH(CH_3)_2C_2H_5$	27–45	
	$(C_2H_5)_2CHCHCH_2CH_2$—CH₃	4–23	
benzodithiole with CH₃ and CH(C₂H₅)₂	$C_6H_5CH_2CH_3$	90	40
	$C_6H_5CH_2CH_2$—CH₃	10	
	$C_6H_5OH†$	Trace	
lactone with C₆H₅, S and oxindole	$(C_6H_5)_2CHCO_2H$ and oxindol‡	—	272

Note: References 265 to 400 are on pp. 525–529.
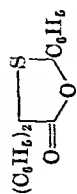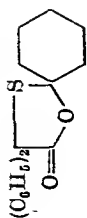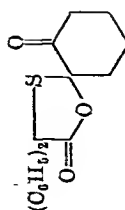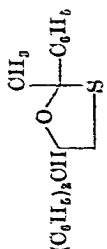
* Products resulting from replacement of sulfur by hydrogen are not shown.
† Acetone was used as the solvent.
‡ Ethanol was used as the solvent.
§ Benzene was used as the solvent.
‖ Acetone or methyl ethyl ketone was used as the solvent.
¶ Benzene or acetone was used as the solvent.

TABLE IV—*Continued*

RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS

Hemithioketal	Product*	Yield, %	Reference
	(a)‡ $(C_6H_6)_2CHCO_2H$ and $(C_6H_6)_2CHCO_2C_2H_6$	—	272
	(b)† $(C_6H_6)_2CHCO_2H$ and C_5H_5CHO	—	
	(a)‡ $(C_6H_6)_2CHCO_2C_2H_6$ and $(C_6H_6)_2CHCH_2OH$	—	272
	(b)† $(C_6H_6)_2CHCO_2H$ and cyclohexanone	—	
	(c)§. $(C_6H_6)_2CHCH_2OH$ and cyclohexanone	—	
	$(C_6H_6)_2CHCO_2H$ and cyclohexanediol‡	—	272
	(a)§ $(C_6H_6)_2CHCH_2CH_3$	81	46
	$p\text{-}CH_3OC_6H_4COCH_3$	72	
	(b)† $(C_6H_6)_2CHCH(CH_3)OCH(CH_3)C_6H_4OCH_3\text{-}p$	42	
	$p\text{-}CH_3OC_6H_4COCH_3$	30	
	$(C_6H_6)_2CHCH(OH)CH_3$	27	
	(a)‖ $C_6H_6COCH_3$	47–71	46
	$(C_6H_6)_2CHCHOHCH_3$	37–62	
	$(C_6H_6)_2CHCH_2CH_3$	19–32	
	$(C_6H_6)_2CHCH(CH_3)OCH(CH_3)C_6H_6$	0–32	
	$(C_6H_6)_2C=CHCH_3$	0–4	
	(b)§ $(C_6H_6)_2C=CHCH_3$	00–06	
	$(C_6H_6)_2CHCH(OH)CH_3$	2–5	

(a)** Cholestan-3-one	64–67	46
3β-Cholestanol	6–19	
3α-Ethoxycholestane	3–13	
3α-Cholestanol	2–12	
Cholestan-3-one	34–58	
3α-Ethoxycholestane	10–31	
3α-Cholestanol	0–18	
(b)§ 3β-Cholestanol	0–14	
Cyclohexanone	54	45
Cholestan-3-one	21	
Cholestan-3β-ol	60	
Cholestan-3-one	56	45
$C_2H_5CH_2CH_2OH$	43	
$C_2H_5CH_2CHO$	/	

Note: References 265 to 490 are on pp. 525–529.
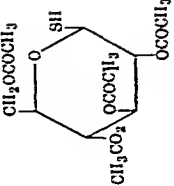
* Products resulting from replacement of sulfur by hydrogen are not shown.
† Acetone was used as the solvent.
‡ Benzene was used as the solvent.
** This experiment was done in acetone solution at various pH values.

TABLE IV—*Continued*

RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS

Hemithioketal	Product*	Yield, %	References
		—	359
	Phenyl-1-thio-β-D-xylopyranoside triacetate	71	362
	2'-Naphthyl-1-thio-β-D-ribopyranoside tribenzoate	73	105
	2'-Naphthyl-1-thio-α-D-arabinopyranoside triacetate	—	363
	Phenyl-1-thio-α-D-arabinopyranoside triacetate	—	363
	Ethyl thio-α-D-glucofuranoside	27	107
	2'-Naphthyl-1-thio-β-D-galactopyranoside tetraacetate	73	264
	Ethyl-1-thio-β-D-mannopyranoside tetraacetate	80	364
	2'-Naphthyl-1-thio-β-lactopyranoside	63	100
	Phenyl-1-thio-β-maltopyranoside heptaacetate	78	100
	Phenyl-1-thio-β-gentiobioside heptaacetate	72	264
	Phenyl-1-thio-β-cellobioside heptaacetate	60	264
	Ethyl thiostreptobiosaminide tetraacetate diethylthioacetal	78	100
	Ethyl dihydrothiostreptobiosaminide pentaacetate	—	365
	3-Thioethyl-3α,9α-oxido-11-ketocholanic acid methyl ester	23	110

(a)‖§§ Cholestan-3-one	46
(C₂H₅)₂CHCHOHCH₂CH₃	46
(b)§ Cholestan-3-one	72
	67
	45–55
(C₂H₅)₂CHCHOHCH₂CH₃O	24–38
(C₂H₅)₂CH(CH₂)₂CH₃	21–30
(C₂H₅)₂CHCHOHCH₂CH₃	17–29

Note: References 205 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.
§ Benzene was used as the solvent.
†† This reaction was run with "isomer A" in methyl ethyl ketone.
‡‡ This reaction was run with "isomer C" in methyl ethyl ketone.
§§ Methyl ethyl ketone solution was used.
‖‖ Benzene-methyl ethyl ketone solution was used.
¶¶ Benzene-n-butanol solution was used.

TABLE IV—*Continued*

RANEY NICKEL DESULFURIZATION OF HEMITHIOACETALS AND HEMITHIOKETALS

Hemithioketal	Product*	Yield, %	References
	(a)†† Cholestan-3-one	78	45
	Cholestan-3β-ol	2	
	(+)-(C₆H₅)₂CHCHOHCH₃	52	45
	(b)‡‡ Cholestan-3-one	80	
	(−)-(C₆H₅)₂CHCHOHCH₃	57	
	(c)§§ Cholestan-3-one	55–00	40
	(C₆H₅)₂CHCHOHCH₃	64–80	
	(d)|||| Cholestan-3-one	80	40
	(C₆H₅)₂CHCH₂CH₃	80	
	(C₆H₅)₂C=CHCH₃	10	
	(e)§ Cholestan-3-one	53–08	40
	(C₆H₅)₂CHCH₂CH₃	60–08	
	(C₆H₅)₂C=CHCH₃	0–20	
	(f)¶¶ Cholestan-3-one	42	40
	C₆H₅CHCHOHCH₃	50–75	

	(C₆H₅)₂CHCOO₂C₂H₅,	—	272
	17β-acetoxy-5α-androstane and		
	3β-hydroxy-17β-acetoxy-5α-androstane		

Strophanthidin-3-acetate ethylenedithioacetal	— —	375
Methyl 12,13 oleanen-23-carboxylate 2-ethylene-thioketal	— —	131
Methyl 2-acetoxy-28-formyl-12,13-oleanene-23-carboxylate ethylenedithioacetal	—	131

B. Dithioketals

n-$C_6H_{13}C(SC_2H_5)_2CH_3$	50	
$CH_3(SCH_2)_3CH_2CO_2C_2H_5$	70	
$[C_2H_5O_2C(CH_2)_5S]_2C_2H_{14}$ n = 4	Good	8
(a)' $C_2H_5O_2C(CH_2)_3CO_2C_2H_5$	58	112
(b)' $C_2H_5O_2C(CH_2)_4CO_2C_2H_5$ n = 5	41	29
n = 8	53	29
(c) $C_2H_5O_2C(CH_2)_4CH=CH(CH_2)_4CO_2C_2H_5$	73	375
		376
		375
$[CH_2O_2C(CH_2)_3C(SC_2H_5)_2CH_3]_2$		
n = 9	—	30
n = 21	—	30
(a)	—	30
(b)' $CH_3O_2C(CH_2)_4CO_2CH_3$	76	112

$\begin{array}{c} (SCH_3)_2 \\ CO_2C_2H_5 \end{array}$ (cyclohexane ring)

Note: References 265 to 490 are on pp. 525–529.

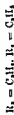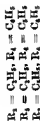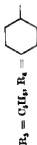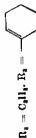* Products resulting from replacement of sulfur by hydrogen are not shown.

ᵃ Degassed Raney nickel was employed.

ᵇ Ethanol was used as the solvent.

ᶜ Raney nickel deactivated by treatment with acetone was used.

ᵈ Hydrogenation over Adams catalyst was employed before isolation.

TABLE V
RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product[a]	Yield, %	References
	A. Dithioacetals		
$CH_2(SC_6H_5)_2$	$(C_6H_5)_2$[b]	9	10
$n\text{-}C_6H_{13}CH(SC_2H_5)_2$		40	8
$C_6H_5CH(SC_2H_5)_2$		65	8
$C_6H_5CH(SCH_2C_6H_5)_2$	$C_6H_5CH=CHC_6H_5 + (C_6H_5CH_2)_2$[b]	—	10
$CH_2[CH(NHCOC_6H_5)CH(SC_2H_5)_2]_2$		—	366
(thiophene CO_2H, SC_2H_5)	$CH_3(CH_2)_3CH(CH_3)CO_2H$	—	373
D-Xylose diethylthioacetal		—	367
D-Glucose diethylthioacetal pentaacetate		60	8
2-Methyl-D-glucose diethylthioacetal tetraacetate		92	368
D-Galactose diethylthioacetal pentaacetate		30	8
D-Altrose diethylthioacetal		97	369
6-Deoxy-L-glucose diethylthioacetal		—	370
L-Fucose diethylthioacetal		68	369
L-Rhamnose diethylthioacetal		85	369
D-Gluco-D-guloheptose diethylthioacetal		—	370
D-Glucosamine diethylthioacetal pentaacetate		—	371
Methyl 3-carbamyl-4-methylnovobioside diethyl-thioacetal		—	372
(phenanthrene structure: CH_3, CO_2CH_3, $CH_2CH(SCH_2C_6H_5)_2$, CH_3O)		—	374

380	—
114	50–70
380a	—
31	83
113	—

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE V—*Continued*

RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product[a]	Yield, %	References
	B. Dithioketals—Continued		
cyclohexane $(SCH_3)_2$, CH_3, $CO_2C_2H_5$		70	112
spiro dithiolane cyclohexane $CO_2C_2H_5$	$(CH_2)_3CO_2C_2H_5$	64	377
decalin OH with dithiane, S	decalin $n\text{-}C_3H_7S$ OH and decalin OH with =O	—	378
octalin $(CH_3)_2$ OH dithiolane S, S		81	379
octalin dithiolane S, S		61	380

		384	—
		118	55
		385	94
		386	—

CH_2CONH_2
$CH_2CONHCH_2CH_3$

$C_7H_{15}S$ SC_7H_{15}

C_7H_{15} SC_7H_{15}

$NCH_2CH_2S(CH_2)_2CH_3$

Note: References 285 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE V—*Continued*

RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product[a]	Yield, %	References
	B. Dithioketals—Continued		
$(C_6H_5CH_2S)_2$		—	381
		—	382
		—	383

$C_6H_5C(SC_2H_5)_2CH_3$ $C_6H_5C(SH)_2CH_2CO_2C_2H_5$ $C_6H_5C(SH)(CH_3)CO_2C_6H_5$ $C_6H_5C(SC_2H_5)_2CO_2H$ $C_6H_5C(SC_2H_5)(C_6H_4)SC_2H_5$			

$C_6H_5CCH_2=CCH_2C_6H_5$	120	—
	8	63
	112	71
	112	79
	8	77
	10	93

$C_6H_5COCH(C_2H_5)CH_3$ and $C_6H_5CHOHCH(C_2H_5)CH_3$	393	—
	394	—
	214	82

Note: References 265 to 490 are on pp. 525–529.
* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE V—Continued

RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product[a]	Yield, %	References
		Good	357
		—	388
Tetrahydrobulduilin		—	389
		—	390, 391
		—	392

18'		22
83'		22
32''		22
50		110
20		8
l		399
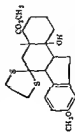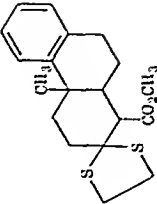
R = CH₃
R = C₂H₅
R = (CH₂)₂Cl

D-Fructose diethyldithioacetal pentaacetate

Note: References 205 to 400 are on pp. 625–629.

* Products resulting from replacement of sulfur by hydrogen are not shown.
' Ethanol was used as the solvent.
' Methanol was used as the solvent.
' 2-Propanol was used as the solvent.

TABLE V—*Continued*

RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

B. Dithioketals—Continued

Substance Desulfurized	Product[a]	Yield, %	References
		—	305
		—	305
		—	306
		58–63	307

	Yield [a]	References
3β,17β-Diacetoxy-5α-androstan-11-one 7-ethylene-thioketal	—	402
3β,17β-Diacetoxy-5-androstene 10-ethylenethioketal	21	128
3β-Acetoxy-5-androstene 17-dibenzylthioketal	—	403
3β,20β-Diacetoxy-5-pregnane 7-ethylenethioketal	85	407
Ethyl 3β-benzoyloxypregnan-21-oate 10-ethylene-thioketal	—	404 405
Pregnane-11-one 3,20-buethylenethioketal	45	400
20β-Acetoxy-5α-pregnane 7-ethylenethioketal	72	404
3β,11α,20-Trihydroxy-5α-pregnane 7-ethylenemetho-ketal	—	129
3β,20β-Diacetoxy-5α-pregnan-11-one 7-ethylene-thioketal	—	129
3β-Acetoxy-5α-pregnane 20-diethylthioketal	52	406
5α-Pregnane 3,20-buethylenethioketal	40	406
Methyl cholanate 3-diethylthioketal	70	252
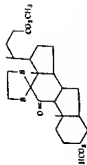
Note: References 265 to 490 are on pp. 525–529.

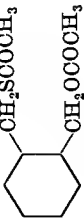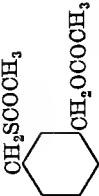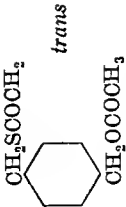[a] Products resulting from replacement of sulfur by hydrogen are not shown.

[b] Deuterated Raney nickel was employed

TABLE V—*Continued*

RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

B. Dithioketals—Continued

Substance Desulfurized	Product[a]	Yield, %	References
17α-Acetoxy-3-methoxyestradiol 16-ethylene-thioketal	and	—	32
17β-Acetoxy-3-methoxyestradiol 16-trimethylene-thioketal		—	32
17α-Acetoxy-3-methoxyestradiol 16-ethylene-thioketal		—	127
17β-Acetoxy-3-methoxyestradiol 16-trimethylene-thioketal		—	400
Dihydrotestosterone acetate 3-o-hydroxyphenyl-thioketal		67	401
3β-Acetoxy-17β-benzoyloxy-5-androstene 7-ethyl-enethioketal	3β-Acetoxy-17β-benzoyloxy-7,7-d_2-5-androstene[b]	50–60	126

Compound	Yield (%)	References[a]
3β-Acetoxyallocholanyl isobutyl ketone ethylenethioketal	95	203
3β-Acetoxy-Δ⁴-norcholenyl isoamyl ketone ethylenethioketal	—	415
3β-Acetoxy-Δ⁴-norcholenyl isoamyl ketone ethylenethioketal	—	415
3β-Acetoxy-Δ⁴-norcholenyl benzyl ketone ethylenethioketal	88	413
Cholest-1-ene 3-ethylenethioketal		
(a)[b] Cholest-1-ene	—	125
(b)[b] Cholest-2-ene	Fair	124
Cholestane	70	417
Cholestane	80	417
3β-Acetoxyallocholane 3-diethylthioketal		
3β-Acetoxyallocholane 3-ethylenethioketal	—	418

Note: References 265 to 400 are on pp. 525–529.

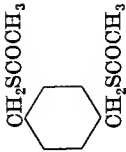[a] Products resulting from replacement of sulfur by hydrogen are not shown.
[b] Dioxane was used as the solvent.
[c] Isoamyl-methyl ethyl ketone was used as solvent.

TABLE V—*Continued*

RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product[a]	Yield, %	References
B. Dithioketals—Continued			
Dehydrocholic acid 3-diphenylthioketal		72	77
Ethyl dehydrocholate 3-diethylthioketal		91	77
3α,6α-Diacetoxycholanic acid 7-ethylenethioketal		—	408
Methyl 3α,7α-diacetoxycholanate 12-ethylene-thioketal		90	414
Methyl 3α-acetoxy-11-ketocholanate 7-ethylene-thioketal		—	409, 410, 411
Ethyl dehydrocholate trisethylenethioketal		—	77
Methyl 3α-acetoxy-11-ketocholanate 12-tri-methylenethioketal		95	123
Methyl 3α-hydroxy-11-ketocholanate 12-tri-methylenethioketal		Good	123
Methyl 3α-carbethoxy-11-ketocholanate 12-tri-methylenethioketal		Good	123
3β-Acetoxy-Δ⁵-norcholenyl methyl ketone ethylenethioketal		69	412
3β-Acetoxy-Δ⁵-norcholenyl ethyl ketone ethylenethioketal		80	412
3β-Acetoxy-Δ⁵-norcholenyl n-propyl ketone ethylenethioketal		98	413
3β-Acetoxy-Δ⁵-norcholenyl isopropyl ketone ethylenethioketal		80	412
3β-Acetoxy-Δ⁵-norcholenyl n-butyl ketone ethylenethioketal		91	413
3β-Acetoxy-Δ⁵-ternorcholenyl n-butyl ketone ethylenethioketal		—	412

3,5-Acetoxy-5α furostane 26-trimethylenethioketal	97	122
3,5-Acetoxy-5α-furostane 12,20-bistrimethylene-thioketal	97	122
Δ⁴-thioxogenone ethylenethioketal	—	422, 423
Thegmone ethylenethioketal	—	424
3,5-Acetoxy-9α,11β-oxido-5α,22β-spiroxtane 7-ethyl-enethioketal	60	139
3,5-Acetoxy-5α,22β-spiroxtan-11-one 7-ethylene-thioketal	—	—
3,5-Spiroxtan-3β-ol-11-one 12-ethylenethioketal	33	207
9(11)-Dehydrohecogenin acetate 12-ethylene-thioketal	88	337
6α-Spiroxtane-24,5β-dioxalylate 15-ethylene-thioketal	—	425
6α-Spiroxtane-3β-ol-11-one 12-ethylene-thioketal	—	420
5α-Spiroxtan-3β-ol-11-one 12-ethylenethioketal	—	421
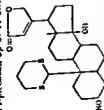
Note: References 203 to 400 are on pp. 425–429.

[a] Products resulting from replacement of sulfur by hydrogen are not shown.
[b] Raney nickel deactivated by treatment with acetone was used.
[c] Deuterated Raney nickel was employed.
[d] Dioxane was used as the solvent.
[e] The product was a mixture of Δ⁴- and 6-cholestene.
[f] W-4 Raney nickel was used in this experiment.
[g] W-2 Raney nickel was used in this experiment.

TABLE V—Continued

RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

B. Dithioketals—Continued

Substance Desulfurized	Product[a]	Yield, %	References
4α,5-Dihydroxycholestane 3-ethylenethioketal		—	419
4β,5-Dihydroxycoprostane 3-ethylenethioketal		—	419
4-Cholestene 3-dibenzylthioketal		92	77
3β-Acetoxy-5α-7,7-d_2-5-cholestene[h]		50–60	126, 103
3β-Acetoxy-5-cholestene 7-ethylenethioketal		—[x]	121
4-Cholestene 3,6-bisethylenethioketal		—	416
Diethyl 3β-cholesterylmalonate 7-ethylene-thioketal		—	121
Δ⁴-Cholesten-6-one 3-ethylenethioketal			
	(a)[i] Cholestan-6-one	—	121
	(b)[d] 4-Cholesten-6-one	—	121
Cholestan-3-one diethylthioketal		91	252
1-Benzylmercaptocholestane 3-dibenzylthioketal		—	125
3β-26-Diacetoxycholestan-22-one 16-ethylene-thioketal		—	419a
Cholestan-6-one 3-ethylenethioketal		—	121
3β-Acetoxycholestan-11-one 7-ethylenethioketal		—	419b
3β-Acetoxy-5α-cholestan-11-one 7-ethylenethioketal		—	402
Cholestane 3,6-bisethylenethioketal		Fair	121
4,4-Dimethyl-5-cholesten-3-one 2-ethylenethioketal		Good[d]	420
3β-Acetoxy-22-ergosten-11-ono 7-ethylenethioketal	3β-Acetoxyergostan-11-one	—	410
5α-Furostane 20-ethylenethioketal		87	122
5α-Furostano 3,26-bisethylenethioketal		69–76	122
3β-Acetoxy-5α-furostane 26-ethylenethioketal		75	122
3β-Acetoxy-5β-furostane 26-ethylenethioketal		75	122
3β-Acetoxy-5-furostene 26-ethylenethioketal		60	122
3β-Acetoxy-5α-furostane 12,20-bisethyl-enethioketal			
	(a)[l] 5-Furostan-3β-ol acetate	74	122
	(b)[m] 5α-Furostan-3β-ol acetate 12-ethylene-thioketal	60	122
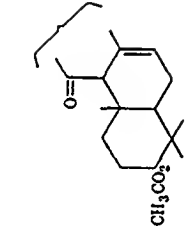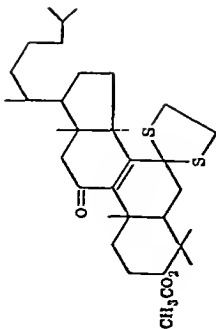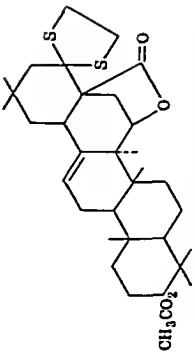
TABLE VI

RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
NH₂CSNH₂	(a) CH₃NH₂	—	1
	(b) NH₂CH=NH	—	134
CH₃(CH₂)₁₆CSNH₂	(n-C₇H₁₅CH₂)₂NH	40	27
		01	20
C₆H₅CSNH₂	C₆H₅CHO	32, 77	430, 133
p-CH₃C₆H₄CSNH₂	p-CH₃C₆H₄CHO	42	430
p-CH₃C₆H₄CSSSNHCH₃	p-CH₃OC₆H₄CHO	45	27
C₆H₅CH₂CSNH₂	C₆H₅CH₂CH₃	90	133
a-C₁₀H₇CSNH₂	a-C₁₀H₇CH₂NH₂	—	1
C₆H₅CH₂CSNHNH₂	C₆H₅CH₂NH₂	82	43
C₆H₅CH₂—NHNCSNH₂	C₆H₅CH—N=CH₂NH₂	—	135
C₆H₅CH₂SC(SH)		23	27
p-CH₃OC₆H₄CSNHCH₂—NSNCSNH₂	p-CH₃OC₆H₄CH=N—N=CH=NH	63	133
(CH₃)₂CSNH₂	m-C₄H₃CHO	32	133
C₆H₅CSNHC₆H₅		15	27
C₆H₅CSNHC₆H₅		40	133
C₆H₅CSNHC₆H₄CH₂OH			27
((CH₃)₂CSNH)₂	((CH₃)₂CHCH₂CHO	53	27
C₆H₅CSNH(CH₂)₂NHC₆H₅			

Note: References 203 to 160 are on pp. 525-529

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE V—Continued

RANEY NICKEL DESULFURIZATION OF DITHIOACETALS AND DITHIOKETALS

Substance Desulfurized	Product[a]	Yield, %	References
B. Dithioketals—Continued			
3-o-Acetylstrophanthidin trimethylenethioketal		—	427
Methyl 3β-acetoxy-11-keto-4,4,14α-trimethyl cholanate 7-ethylenethioketal		—	429
		—	130
3β-Acetoxylanostan-11-one 7-ethylenethioketal		—	428
3β,11-Diacetoxylanostane 7-ethylenethioketal		—	130
Methyl 12(13)-oleanene-23-carboxylate 2-ethylenethioketal		—	131
		Good	132

Note: References 265 to 400 are on pp. 525–529.

[a] Products resulting from replacement of sulfur by hydrogen are not shown.

N(CSNC₅H₁₀)₂	38	27
morpholine—CH₂CSN (quinoline)	40	27
(benzothiophene-S structure)	—	432
C₆H₅CH₂CSN morpholine	—	38
m-CH₃OC₆H₄CH₂CSN morpholine	69	27
p-CH₃OC₆H₄(CH₂)₂CSN morpholine	65	27
2-C₄H₃CH₂CSN morpholine	63	27

C₆H₅CH₂, or C₆H₅CH₂CH₂N morpholine

(pyridine) CH₃ (?)

Note. References 205 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE VI—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
p-HOC$_6$H$_4$CSNHC$_6$H$_5$	p-HOC$_6$H$_4$CHO	78	133
C$_6$H$_5$CSNHC$_6$H$_5$	C$_6$H$_5$N=CHNHC$_6$H$_5$	50, 86	27
(C$_6$H$_6$NH)$_2$CS		—	61
(C$_6$H$_6$O)$_2$CHCSNH$_2$		10	27
C$_6$H$_{11}$CSNH— (cyclohexyl)	C$_6$H$_6$CH$_2$CH$_3$ or C$_6$H$_6$CH$_2$CH$_2$NH— (cyclohexyl)	—	36
C$_6$H$_6$CH$_2$CSNH(CH$_2$)$_2$C$_6$H$_5$	C$_6$H$_5$CH$_2$CH$_2$N— (piperidine) or	34	27
C$_6$H$_5$CH$_2$CSN— (piperidine)	H$_5$C$_2$N— (piperidine)	63	27
		44	
p-C$_6$H$_5$C$_6$H$_4$CH$_2$CSN— (piperidine)		73	27
2-C$_{10}$H$_7$CH$_2$CSN— (piperidine)		50	27
(pyridyl)CH$_2$CSN— (morpholine)		41	431

(a) (C_2H_5) NH O N H	—	84, 85	135
(b) (C_2H_5) N O N H			130, 137
(c) (C_2H_5) N O N H +			431
(d) (C_2H_5) N S O N H + $N-C_2H_5$ O N H			141
(e) (C_2H_5) N OH O N H	—		
(f) (C_2H_5) NH O N H	—	70	139

$$R_3 = R_4 = \text{cyclopentyl}$$
$$R_3 = R_4 = C_2H_5$$

Note: References 265 to 490 are on pp. 525–539.

* Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE VI—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
(cyclohexylphenyl morpholino thioamide)		57	27
p-$C_6H_5C_6H_4CH_2CH_2CSN$ (morpholine)		63	27
$(NCSCH_2C_6H_4—)_2$ morpholino		72	27
2,4-Dimethyl-5-carbethoxy-3-morpholinoethyl-pyrrole		72	433
$R_3 = CH_3$	(a) $CH_3CH(NHCHO)_2$	—	137
	(b) Oil	—	141
$R_2 = COOCH_3$		—	435
$R_3 = C_6H_5$	Oil	—	141
$R_2 = COC_6H_5$		—	435
$R_3 = R_4 = OH_3$	$(CH_3)_2CH(NHCHO)CONH_2$ (?)	—	141
$R_2 = COOH_3$, $R_3 = OH_3$		—	435
$R_3 = CH_3$, $R_4 = C_6H_5$		21	136
$R_2 = CH_3$, $R_3 = C_6H_5$		46	136
$R_2 = O_2H_5$, $R_3 = O_6H_5$		—	435
$R_2 = COOCH_3$, $R_3 = OH_2C_6H_5$			

Structure: pyrrole ring with substituents R_1, R_3, R_4, NR_2 and $O{=}$, ${=}S$

$R_3 = R_4 = CH_3$	30	136
$R_3 = R_4 = $ [structure]	26	136
$R_3 = R_4 = $ [structure] CH_3	40	136
$R_3 = R_4 = $ [structure]	43	130
$R_1 = CH_3, R_3 = R_4 = $ [structure]	17	130
$R_1 = CH_3, R_3 = R_4 = $ [structure]	55	130
$R_1 = R_3 = CH_3, R_4 = R_6 = $ [structure]	7	136
$R_1 = R_3 = CH_3, R_4 = R_6 = C_2H_5$	38	136

$R_6 = C_3H_7$¶

Note: References 265 to 490 are on pp 625–629.

* Products resulting from replacement of sulfur by hydrogen are not shown.
† Ethanol containing sodium ethoxide was used as the solvent.
‡ Ammoniacal ethanol was used as the solvent.
§ The ratio by weight of compound to Raney nickel was 1.5
¶ The ratio by weight of compound to Raney nickel was 1.2.
** With methanol, propanol, or cyclohexane in place of ethanol as solvent the normal desulfurization product ($R_3 = H$) was obtained in 48% yield.
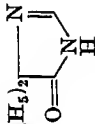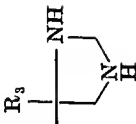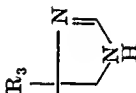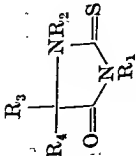
TABLE VI—Continued

RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
$R_3 = R_4 = C_6H_5$ (continued)	(g)† $(C_6H_5)_2$ ...	75	
	(h)‡ Mixture of (f) and (g)	—	140
	(i)§ R_3, R_4 ... NH ... N/H	—	
	(j)‖ R_3, R_4 ... N/H		
$R_3 = R_4 = p\text{-}CH_3OC_6H_4$		22	136
$R_2 = R_3 = CH_3$, $R_4 = C_6H_5$		10	136
$R_2 = CH_3$, $R_3 = R_4 = $ ⬠		—	136
$R_2 = CH_3$, $R_3 = R_4 = C_6H_5$		—, 41	136
$R_1 = R_2 = R_3 = CH_3$, $R_4 = C_6H_5$		—	136

$CH_3CH(C_6H_5)CONHCH_3$

$$\underset{\substack{R_4 \\ O}}{\overset{R_3}{C}}\text{—}\underset{R_1}{\overset{NR_2}{N}}\text{—}\underset{}{\overset{OR_5}{N}} \longleftarrow \underset{\substack{R_4 \\ O}}{\overset{R_3}{C}}\text{—}\underset{R_1}{\overset{NR_2}{N}}\text{=S}$$

$R_1 = CH_3, R_2 = R_4 =$ [structure]

46   136

$R_1 = CH_3, R_2 = R_3 = C_2H_5$
$R_1 = R_3 = CH_3, R_2 = R_4 = C_2H_5$

58   130
43   136

$(C_2H_5)_2$ [structure] NH

439

** [marks]

[reaction arrow] R_2CHCOR,
R_2NCHO

$R_1 = CH_3, R_2 = R_3 = C_2H_5$
$R_1 \ldots R_3 = C_2H_5$
$R_2 = 2\text{-}C_3H_7, R_4 = R_3 = C_2H_5$
$R_3 = R_2 = C_3H_7$

74   437
86   437
58   437
49   437

[piperidine-thione structure]

13   438

Note: References 205 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

** Desulfurization was not observed.

TABLE VI—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
RCH=C(=O)–NH–C(=S)–N(H) (ring)	RCH₂CH(NHCHO)CONH₂		
R = CH(CH₃)₂		—	137
R = CH₂CO₂CH(CH₃)₂		—	137
R = C₆H₅		—	137
R = p-HOC₆H₄		—	137
R = p-CH₃OC₆H₄		—	137
R = 3,4-CH₂O₂C₆H₃		—	137
R = p-ClC₆H₄		—	137
R = (indole)	(indole)CH₂CH(NHCHO)CONH₂	—	137
R₁ = R₃ = CH₃, R₄ = C₆H₅		44	136

Thioamide structures:

$RCH=C$ with NH, $C=S$, ring $N{-}H$, O

$R = CH(CH_3)_2$
$R = CH_2CO_2CH(CH_3)_2$
$R = C_6H_5$
$R = p\text{-}HOC_6H_4$
$R = p\text{-}CH_3OC_6H_4$
$R = 3,4\text{-}CH_2O_2C_6H_3$
$R = p\text{-}ClC_6H_4$

$R = $ (indole, N–H)

Product: $RCH_2CH(NHCHO)CONH_2$

(indole)$CH_2CH(NHCHO)CONH_2$

R_4R_3C with $S=$, NR_2, $C=O$, $N{-}R_1$

$R_1 = R_3 = CH_3, \ R_4 = C_6H_5$

$R_1 = R_3 = C_2H_5, R_2 = C_4H_9$		138
$R_1 = R_2 = CH_3, R_3 = C_2H_5$	—	138
$R_1 = C_2H_5, R_2 = C_2H_5, R_3 = C_2H_5$	—	138
$R_1 = R_3 = C_2H_5, R_2 = C_4H_9$	—	138

$R_3 = C_6H_5, R_2 = $

$R_1 = R_3 = CH_3, R_2 = C_6H_5$	—	138

$R_3 = C_6H_5, R_2 =$

$R_1 = CH_3, R_2 = CH_3$	—	138
$R_1 = C_6H_5, R_2 = C_2H_5$	—	138
$R_1 = C_6H_5, R_2 = m-CH_3C_6H_4$	—	138
$R_1 = C_6H_5, R_2 = p-ClC_6H_4$	—	136

$R_3 = C_6H_5, R_2 =$

structure		
(a) $R_5 = CH_3$	44‡‡	141
(b) $R_5 = C_2H_5$	48‡‡	141
(a) $R_5 = n-C_3H_7$	41§§	141
(b) $R_5 = n-C_4H_9$	30††	138
(a) $R_5 = CH_3$	—	138
(b) $R_5 = C_2H_5$	—	133
$R_5 = CH_3$	—	138

$R_4 = R_5 = CH_3$

$R_4 = R_5 = C_2H_5$

$R_4 = C_2H_5, R_5 = C_2H_5$

$R_1 = CH_3, R_2 = C_4H_9, R_3 = C_2H_5$

$R_1 = H, R_2 = C_2H_5, R_3 = C_2H_5$

Note: References 205 to 490 are on pp. 625–529.

† Product resulting from replacement of sulfur by hydrogen are not shown.
‡‡ No distilled product was isolated.
‡ This experiment was run with the alcohol R_2OH as solvent and a 30-minute reflux period.
§§ This experiment was run with the alcohol R_2OH as solvent and a 4-hour reflux period. An extended reaction time affected the expected product of desulfurization.

TABLE VI—Continued
RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
R = C₂H₅		37	141
R = C₆H₁₁-i		58	141
R = C₆H₅		—	138, 141††
R = CH₂C₆H₅		00	141
R₁ . . . R₄ = H		—	436
R₁ = R₂ = C₆H₅		—	430
R₃ = R₄ = C₂H₅		70	141
R₃ = C₂H₅, R₄ = C₆H₁₁-i		71	141
R₂ = C₆H₅, R₃ = C₂H₅, R₄ = C₆H₅		—	138
R₃ = C₂H₅, R₄ = (cyclohexyl)		—	138

TABLE VII

Raney Nickel Desulfurization of Thiol Esters

A. Formation of Aldehydes, Hydrocarbons, and Sulfides*

Thiol Ester	Aldehyde (%)	Hydrocarbon (%)	Sulfide (%)	References
$CH_3COSC_2H_5$	73			441
$CH_3COSC_2H_5$		(a) Biphenyl (29)†		15
		(b) Biphenyl (47) and toluene (10)‡		11
$CH_3CH_2COSC_2H_5$	80			441
$CH_3(CH_2)_2COR$§	—			442
$CH_3(CH_2)_3COR$§	—			442
$CH_3(CH_2)_4COR$§	~92			442
$CH_3(CH_2)_{10}COSC_2H_5$	49			442, 441
$(CH_2COSC_2H_5)_2$	70			441
$(CH_2CH_2COSC_2H_5)_2$	77			441
$(CH_2CH_2CH_2COSC_2H_5)_2$	66			441
$CH_3O\!\!\overset{(CH_2)_3}{\diagdown\!\!\!\diagup}\!\!COSC_2H_5$	34			149

Note: References 285 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.
† Raney nickel degassed at 200° was used.
‡ This reaction was run in benzene solution at 220° with Raney nickel degassed at 500°.
§ $R = SC_2H_5$ or $SCH_2C_6H_5$.

TABLE VI—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOAMIDES

Thioamide	Product*	Yield, %	References
		72,‖‖ 95	162, 440

Note: References 205 to 400 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown.

‖‖ Raney cobalt and ethanol-dimethylformamide were used.

		441, 150a, 146
C₆H₅COSC₂H₅	(a) 51, 60, 62	15
C₆H₅COSC₆H₅	(b) Biphenyl (28)†	15, 11
	(a) Biphenyl (40)‡	11
C₆H₅COSCH₂C₆H₅	(c) Biphenyl (37–50)	15
	(C₆H₅CH₃, 8)	
	(b) (C₆H₅)₂S (71, 30)†	411
	(C₆H₅)₂S (74)‡	411
	C₆H₅SCH₂C₆H₅ (45)	441
	and (C₆H₅)₂S (—)†	313
		273
		273
		441
C₆H₅COSC₂H₅	70	15
C₆H₅CH=CHCOSC₂H₅	C₆H₅CH₂CH₂CHO (45)	
C₆H₅CH₂CH₂COSC₂H₅	81	
CH₃CH₂CH₂COOCH₂CH₂SCOCH₃	92	
di-OH₂CH₂(OH)CH₂OCOCH₂CH₂SCOCH₃	— —	
(—)C₆H₄CH(OH)CH₂OCOCH₂CH₂SCOCH₃	60	
1-C₁₀H₇COSC₂H₅	((C₆H₅)₂S (23),	
1-C₁₀H₇SCOC₆H₅	1-C₄H₇SC₆H₅ (33), and	
	(1-C₄H₇)₂S (20)†	
	(1-C₄H₇)₂S (20),	
	(a) (C₆H₅)₂S (30),	
	2-C₆H₅C₆H₄ (42), and	
	(2-C₆H₅)₂S (39)†	15
2-C₆H₅SCOC₆H₅	(b) (2-C₆H₅)₂, (60),	11
	2-C₆H₅C₆H₄ (18),	
	C₆H₅C₆H₄ (—)**	

Note: References 283 to 490 are on pp. 525–529.

* Products resulting from replacement of sulfur by hydrogen are not shown

† Raney nickel degassed at 200° was used.

‡ Raney nickel degassed at 100° was used.

¶ This reaction was run in xylene at 189° or 200° with Raney nickel degassed at 500°

** Raney nickel degassed at 200° was used without solvent at 200°.

TABLE VII—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOL ESTERS

A. *Formation of Aldehydes, Hydrocarbons, and Sulfides*—*Continued*

Thiol Ester	Aldehyde (%)	Product Hydrocarbon (%)	Sulfide (%)	References
cyclohexane–CH₂SOOCH₃ / CH₂OCOCH₃		cis (50) trans (40)		144
cyclohexane–CH₂SCOCH₃ / CH₂OCOCH₃		cis (76) trans (48)		144
cyclohexane–CH₂SCOCH₂ *trans* CH₂OCOCH₃		60		144
cyclohexane–CH₂SCOCH₃ / CH₂SCOCH₃		cis (17) trans (20)		144
cyclohexane–CH₂SCOCH₃ / CH₂SCOCH₃		cis (23) trans (11)		144

COSC₂H₅

HCOCOCH₃

HCOCOCH₃   146

	Yield, %	References
CH₂OCOCH₃		444
Ethyl 3β-acetoxythiocholanate	50–65††	154
Ethyl 3α-formoxythiocholanate	39	154
Ethyl 3β-acetoxy-5-thiocholenate	78	444
Ethyl 3α-acetoxy-11-thiocholenate	50–55††	154
Ethyl 12α-acetoxythiocholanate	83	154
Ethyl 3α,12α-diacetoxynorthiocholanate	64	154
Ethyl (or benzyl) 3α,12α-diformoxythiocholanate	69	147
	60–80††	

B. Preparation of Alcohol‡‡

Thiol Ester	Product*	Yield, %	References
n-C₃H₇COSCH₂C₆H₅		—	152
n-C₅H₁₁COSCH₃		80–98	153
CH₃O₂C(CH₂)₄COSCH₃		—	153
CH₃O₂C(CH₂)₁₀COSC₆H₅		—	416

Note: References 205 to 490 are on pp. 825–829.

* Products resulting from replacement of sulfur by hydrogen are not shown.
†† Nickel that had had been deactivated gave the alcohol rather than the aldehyde.
‡‡ The yield is based on the formation of alcohol unless otherwise noted.

TABLE VII—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOL ESTERS

A. Formation of Aldehydes, Hydrocarbons, and Sulfides*—Continued

Thiol Ester	Product			References
	Aldehyde (%)	Hydrocarbon (%)	Sulfide (%)	
$C_6H_5COSCH_2CHCO_2H$ (N-phthalimido)		40		143
(thiochromone, $R_1 \ldots R_6$)		$R_1 \ldots R_4 = H$		151
$R_1 \ldots R_6 = H$		$R_1 = R_4 = H$		151
$R_1 = CO_2H$		$R_1 = CH_3$		151
$R_1 = CO_2H, R_2 = CH_3$		$R_3 = R_4 = CH_3O$		151
$R_1 = CO_2H, R_4 = R_5 = CH_3O$		$R_2 = R_3 = CH_3O$		443
$R_1 = CO_2H, R_3 = R_4 = CH_3O$				
$R_1 = CO_2H, R_3 = R_4 = CH_2$(O,O)		$R_2 = R_3 = CH_2$(O,O) (12)		443

Reactant	Product	Yield (%)	Refs.
COSCH₂C₆H₅ / CH₃ / NO₂ (ring)	CH_2OH / CH_3 / NH_2 (ring)	—	47
CO₂CH₃ / COSC₆H₄CH₃-p	(bicyclic CO, CH₃)	—	150a
CH₃COSCH₂C₆H₅ / CH₃ / NO₂ (ring)	CH_2CH_2OH / CH_3 / NH_2 (ring)	—	47
3,4,5-(CH₃O)₃C₆H₂COSC₆H₄CH₃-p	1,2,3-(CH₃O)₃C₆H₂CH₃	20–30	52
C₆H₅COSCH₂C₆H₅	3,4,5-(CH₃O)₃C₆H₂CH₂OH	40	152
(CH₃)₃(COSCH₂C₆H₅)₃			152
C₆H₅COSCH₂C₆H₅			150a
p-CH₃C₆H₄SCO (biphenyl) CO₂H		—	440
2-C₆H₅C₂H₄COSCH₂C₆H₅ (pyridine) COSCH₃		52, 82	153, 447

Note: References 205 to 490 are on pp 525–559.

‡‡ The yield is based on the formation of alcohol unless otherwise noted.

TABLE VII—Continued

RANEY NICKEL DESULFURIZATION OF THIOL ESTERS

B. Preparation of Alcohols‡‡

Thiol Ester	Product	Yield, %	References
R = H	$C_6H_5CHOHCO_2H$	54	269
R = CH₃	$m\text{-}CH_3C_6H_4CH(OH)CO_2H$	70	269
Methyl 7-methylbisdehydrothiodoisynolate		—	448
		76–87	155, 156
		39	155, 156
Methyl 3β-acetoxy-5α-thioetiocholanate		93	153
Methyl 3β-acetoxy-5β-thioetiocholanate		—	153
Benzyl 12,13-oleanen-30-thiolate		90	157
Methyl 2-acetoxy-12,13-oleanen-28-thiolate		87	451
Methyl 2-acetoxy-10,11-ursen-12-one-28-thiolate		—	452
Methyl 2,29-diacetoxythioeelinoeyslate		—	453

Note: References 205 to 490 are on pp. 525–529.

‡‡ The yield is based on the formation of alcohol unless otherwise noted.

TABLE VIII

RANEY NICKEL DESULFURIZATION OF ISOTHIOURONIUM SALTS

Isothiouronium Salt	Product[a]	Yield, %	Reference
$CH_3CH_2SC(CH_2)_4CH_2SC$ $\overset{\oplus}{N}H_2$, Cl$^\ominus$ NH_2		—	326
		84	159
		70	158
		—	453a

Note: References 265 to 490 are on pp. 525–529.

[a] In each example reported, desulfurization involved only replacement of sulfur by hydrogen.

TABLE VIII—Continued

RANEY NICKEL DESULFURIZATION OF ISOTHIOURONIUM SALTS

Isothiouronium Salt	Product*	Yield, %	Reference
S-(Tetraacetyl-β-ᴅ-glucopyranosyl) isothiouronium bromide		—	454
ᴅ-Glucose θ-isothiouronium iodide 1,2,3,4-tetraacetate		55	455
3β,5α-Dihydroxycholestane θ-isothiouronium p-toluenesulfonate		88–95	456

Note: References 205 to 490 are on pp. 525–529.

* In each example reported, desulfurization involved only replacement of sulfur by hydrogen.

TABLE IX

Raney Nickel Desulfurization of Thiophenes and Thiazoles

A. Thiophenes[a]

Substance Desulfurized	Product	Yield, %	References
$R_1, R_4 = H$ $B_1 = CO_2H$	$CH_3CHClCH_2CH_2CH_3$	65	160, 50
	(a) $CH_3(CH_2)_3CO_2H$ and $HO_2C(CH_2)_3CO_2H$	Poor[b]	14
	(b) $CH_3(CH_2)_5CO_2H$	70.[c]	457, 200
	(c) $CH_3D(CH_2)_3CH_2CO_2H$	71[d]	188
	(d) $CH_3D_2(CH_2)_3CT_2CO_2H$		155
	(e) $CH_3(CH_2)_3CHO$		43, 14
	$CH_3(CH_2)_3OH$ and CH_3CHO		
	(f) CH_3CHO and $CH_3CO(CH_2)_2COCH_3$		104
	(g) CH_3CHO, $CH_3COCH(CH_2)_3CH_3$, and $CH_3COC(CH_2)_2COCH_3$		104
$B_1 = COCH_3$			

Note: References 205 to 490 are on pp. 525–529.

[a] Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

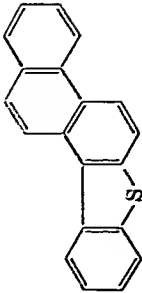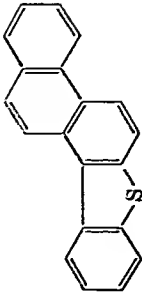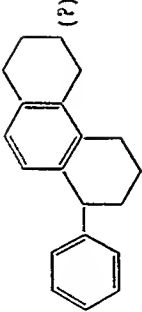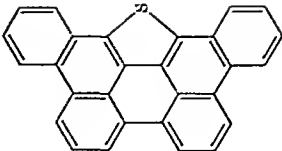[b] Aqueous sodium carbonate was used as the solvent.

[c] W-7 Raney nickel was used.

[d] W-6 Raney nickel was used.

[e] Deuterium oxide and Raney nickel were employed.

[f] Tritiated water was used in the reaction.

TABLE IX—Continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
$R_4 \underset{R_5}{\overset{R_3}{\fbox{}}} \underset{S}{} R_2$ R_3 (continued)	*A. Thiophenes—Continued*		
$R_2 = CH_2CO_2H$	$CHT_2(CHT)_2CT_2CH_2CO_2H$	—[g]	165
$R_2 = CHOHCO_2H$ (*d* and *l*)		—	458
$R_2 = C(=NOH)CO_2H$		50[b]	175
$R_2 = CH(NH_2)CO_2H$	$CH_3(CH_2)_3CH(NH_2)CO_2H$	59[b]	175
$R_2 = \overset{O}{\underset{O}{CH}}$		42	184b
$R_2 = COC_2H_5$	$C_2H_5COC_4H_9\text{-}n$ and $C_2H_5CO(CH_2)_8COC_2H_5$ (?)	—	14
$R_2 = CH=CHCO_2H$	$CH_3(CH_2)_5CO_2H$	36	209
	$CHT_2(CHT)_2CT_2(CHT)_2CO_2H$	—[g]	165
$R_2 = CH(NH_2)CH_2CO_2H$		79	176
$R_2 = CH(CO_2H)CH_2CO_2H$ and the (+) isomer		—	257
$R_2 = CO(CH_2)_2CO_2H$	(*a*) $O=\fbox{}\text{---}C_4H_9\text{-}n$	—	14
	$O=\fbox{}(CH_2)_8\fbox{}=O$ (?)	—	
	$n\text{-}C_4H_9CO(CH_2)_2CO_2H$	—	
	$HO_2C(CH_2)_2CO(CH_2)_8CO(CH_2)_2CO_2H$ (?)	—	

	Yield	Ref.
$R_1 = CO(CH_2)_2CO_2H$	—	269
(h) $n\text{-}C_5H_{11}CO(CH_2)_2CO_2H$ and	57ᵃ	164
	73ᵇ	163
	Fair	14
$R_4 = CH_2(CH_2)_2CO_2H$		
(c) $n\text{-}C_5H_{11}CO(CH_2)_2CO_2H$	Trace	209
(a) $n\text{-}C_6H_{13}CO_2H$	60	182
(b) $HO_2C(CH_2)_{16}CO_2H$	54	177
	41	184ᵇ
$R_5 = CH(OC_2H_5)_2$	49	165
$R_6 = CH_2N(C_2H_5)_2$		
$R_7 = COC_2OC_2H_5$		
$R_8 = C(OH)(CH_2)_5(CH_2)_2CH_3$		
(a) 4-Methyl-4-octanol	82	182
(e) C_9H_{20} (?)	—	210
(e) $CH_3(CH_2)_4CH(CH_3)CH(CH_3)_2$	61	14
	25	
$R_6 = CH_2OCH_2CH_2CH(CH_3)_2$	47–50	
$R_7 = CH_2C_6H_5$	75, —	457, 459
$R_8 = COC_2H_5$		
(c) $C_6H_5COCH_2C_6H_5$	50	182
$C_6H_5OCH_2CH_2COC_2H_4$		
(b) $C_6H_5COC_2H_5\text{-}n$		

$R_1 = CH_2OCH_2CH_2 \underset{S}{[]} CH_3$


Note: References 265 to 490 are on pp. 525–529.

* Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

ᵃ Aqueous sodium carbonate was used as the solvent.

ᵇ The starting material was subjected to dehydration conditions before desulfurization.

ᶜ Tritiated water was used in the reaction.

TABLE IX—Continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

A. Thiophenes[a]—Continued

$$R_4 \underset{R_5\ \ S\ \ R_2}{\overset{R_3}{\bigcirc}} R_2 \text{ (continued)}$$

Substance Desulfurized	Product	Yield, %	References
$R_3 = CH=C(C_6H_5)CO_2H$	$n\text{-}C_4H_9CH(C_6H_5)CO_2H$	75[b]	108
$R_2 = CO(CH_3)_2CO_2H$	$n\text{-}C_4H_9CHOH(CH_2)_8CO_2H$	—	269
$R_2 = CH_2(CH_3)_{14}CH_3$	5-Eicosanol	Fair	185
$R_2 = CO(CH_3)_{14}CH_3$		90	185
$R_3 = C(C_6H_5)_3$		—	183
$R_2 = CO_2H, R_4 = NO_2$	$CH_3CH(NH_2)CH_2CH_2CO_2H$	—	184f
$R_3 = CO_2H, R_5 = CH_3$		68	269
$R_3 = CO_2H, R_4 = CH_3$		60	269
$R_2 = CO_2H, R_5 = OCH_2$		82[h]	258
$R_2 = CO_2H, R_3 = OCH_2$		Fair	400
$R_3 = CO_2H, R_3 = C_3H_5$		—	259
$R_3 = CH(NH_2)CO_2H, R_5 = CH_3$	(a) $H_2N(CH_2)_4CO_2H$	53[b]	174, 175
	(b) $CH_3CONH(CH_2)_4CO_2H$	—[b]	108
$R_2 = CO_2H, R_5 = NHCOCH_3$	$CH_3CH(NH_2)(CH_2)_4CO_2H$	—[b]	184a
$R_2 = CO_2H, R_4 = NHCOCH_3$	$n\text{-}C_4H_9COOH$, and $CH_3CO(CH_2)_8COOH$	—[b]	108
$R_3 = COCH_3, R_5 = SCH_3$		Poor	373
$R_2 = CH(NH_3)CH_2CO_2H, R_5 = CH_3$		41[b]	176
$R_2 = CH(NH_3)CO_2H, R_5 = C_2H_5$		—	174, 175
$R_2 = COCH_3, R_5 = C_2H_5$		25[b]	14
$R_2 = CO(CH_2)_3CO_2H, R_5 = Br$	$n\text{-}C_3H_7CO(CH_2)_3CO_2H$	—	104
$R_3 = CO_2H, R_3 = CH(CH_3)_2$		—	461
$R_3 = CO_2H, R_4 = CH(OH_3)_2$		—	461

Compound		
$R_1 = CO_2H,\ R_2 = C(CH_3)_3$	70^d	170
$R_1 = ClO,\ R_2 = n\text{-}C_3H_7$	65	34
$R_1 = CO_2H,\ R_2 = (CCH_3)_3$	50	34
$R_1 = CH_2(CH_3)_3,\ R_2 = CH_3$	46	177
$R_1 = CH(NH_2)CO_2H,\ R_2 = CH_2(CH_2)_2CO_2H$	83	49
$R_1 = CH_2CH_2CO_2H,\ R_2 = C_2H_5$	51^b	163
$CH_3(CH_2)_3CH_2OH$		
$(CH_3)_2CH(CH_2)_2CH_2OH$		34
5-Decanol	—	
$R_1 = CH_3,\ R_2 = $		
$R_1 = CH_2CH_2OH,\ R_2 = CH_2N(C_2H_5)_2$	44	178
$R_1 = CH(OH)CH_3,\ R_2 = n\text{-}C_4H_9$	88	1846
$R_1 = CH_2(CH_2)_3CO_2H,\ R_2 = CH_3NHCOCH_3$	83	462
$R_1 = CH_2(CH_2)_4CO_2H,\ R_2 = CH_3NHCOCH_3$	72	462
$R_1 = CH(NHCOCH_3)CH_2CO_2H,\ R_2 = C_2H_4$	77	170
$R_1 = CH_2NH_2CO_2H,\ R_2 = CH_2(CH_2)_3CO_2H$	—	40
$R_1 = COCH_3,\ R_2 = $ COOCH$_3$	91	185
$R_1 = CH_2N(C_2H_5)_2,\ R_2 = C_2H_5$	54	177
$R_1 = CH_2CH_2OH,\ R_2 = C_6H_{11}$	50	178

Note: References 265 to 490 are on pp. 525–529.
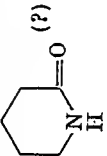
*Products derived from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

[b] Aqueous sodium carbonate was used as the solvent.
[c] Aqueous sodium bicarbonate was used as the solvent.
[d] Aqueous sodium hydroxide was used as the solvent.

TABLE IX—Continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References

R$_4$ ⟩—R$_3$ (continued)
R$_6$—S—R$_2$

A. Thiophenes—Continued

R$_2$ = CH$_2$(CH$_2$)$_2$CO$_2$H, R$_5$ = C(CH$_3$)$_3$		—'	171
R$_2$ = CH$_2$(CH$_2$)$_6$CO$_2$H, R$_5$ = CH(NHCOCH$_3$)CH$_3$	CH$_3$CH(NHCOCH$_3$)(CH$_2$)$_8$CO$_2$H	50	184c
R$_2$ = CH(OC$_2$H$_5$)$_2$, R$_5$ = n-C$_4$H$_9$	n-C$_8$H$_{17}$CH(OC$_2$H$_5$)$_2$ and n-C$_9$H$_{19}$OC$_2$H$_5$	—	182
R$_2$ = CH$_2$(CH$_2$)$_4$CO$_2$H, R$_5$ = CH$_2$NHCOCH$_3$		65	402
R$_2$ = CH$_2$CH(CH$_3$)CH$_2$CO$_2$H, R$_5$ = CH$_2$NHCOCH$_3$		62	402
R$_2$ = C$_2$H$_5$, R$_5$ = COC$_6$H$_{13}$-n		90	104
R$_2$ = CH$_2$(CH$_2$)$_3$CO$_2$H, R$_5$ = CH(NHCOCH$_3$)CH$_3$	CH$_3$CH(NHCOCH$_3$)(CH$_2$)$_5$CO$_2$H	49	184c
R$_2$ = C(NOH)(CH$_2$)$_3$CO$_2$H, R$_5$ = CH$_2$(CH$_2$)$_3$CO$_2$H	HO$_2$C(CH$_2$)$_3$CH(NH$_2$)(CH$_2$)$_3$CO$_2$H and	—	40

HO$_2$C(CH$_2$)$_7$ ⟨ring⟩ N—H =O (?)

R$_2$ = CH$_2$C$_6$H$_4$CO$_2$H-p, R$_5$ = CO$_2$H		—'	107
R$_2$ = CH(NHCOCH$_3$)CH$_2$CO$_2$H, R$_5$ = C(OH)$_3$		55	170
R$_2$ = CH$_2$OH, R$_5$ = C$_6$H$_5$		—'	403
R$_2$ = CH$_2$CH$_2$C$_6$H$_4$CO$_2$H-p, R$_5$ = CO$_2$H		—'	107
R$_2$ = CH$_2$(CH$_2$)$_4$CO$_2$H, R$_5$ = CH(NHCOCH$_3$)CH$_3$	CH$_3$CH(NHCOCH$_3$)(CH$_2$)$_{10}$CO$_2$H	24	184c
R$_2$ = CH$_2$(CH$_2$)$_2$C$_6$H$_5$, R$_5$ = CO$_2$H		—'	403
R$_2$ = CH$_2$(CH$_2$)$_3$C$_6$H$_5$, R$_5$ = CO$_2$H		—'	403
R$_4$ = CH$_2$(CH$_2$)$_2$C$_6$H$_4$CO$_2$H-p, R$_5$ = CO$_2$H		—'	403
R$_2$ = CH$_2$(CH$_2$)$_2$CO$_2$H, R$_5$ = CH$_2$C$_6$H$_5$		—'	171

R₂ = CH=C(C₂H₅)CO₂H, R₃ = C₂H₅			108
R₃ = CH₃, R₁ = C₅H₁₁ⁿ		03	185
R₁ = CH₂(CH₂)₃CO₂H, R₃ = C₂H₅		82	104
R₃ = CH₂(CH₂)₄CO₂H, R₂ = CH₂C₆H₅		—	100
R₂ = CH₂(CH₂)₃CO₂H, R₄ = CH₂CH₂C₆H₅	*n*-C₅H₅CH(CH₃)₂CO₂H	ᶜ	171
R₁ = CH₂(CH₂)₃CH₂CO₂H, R₂ = CO₂H		ᶜ	463
R₁ = CH₂(CH₂)₃CO₂H, R₂ = CH₂(CH₂)₂CO₂H		—	105
R₁ = CH₂(CH₂)₃CO₂H, R₂ = CH₂(CH₂)₃CH₂	CH₃CH₂CH₂CT₂CH(T)CT₂CT₂CO₂H	ᶜ	105
R₁ = CH₂(CH₂)₃CO₂H, R₂ = CH₂(CH₂)₃CH₂		ᶜ	160
R₁ = C₂H₅ⁿ, R₂ = CO(CH₂)₄CO₂H		—	450
R₁ = CH₂(CH₂)₃CO₂H, R₃ = CH₂(CH₂)₄CO₂H		—	108
R₁ = CH₂(CH₂)₃CO₂H, R₂ = CO₂H		—	172
R₁ = CH₂(CH₂)₃CO₂H, R₂ = C₅H₁₁ⁿ		90ᵇ	104

Note: References 205 to 490 are on pp. 525–529.

a Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.
b Aqueous sodium carbonate was used as the solvent.
c Tritiated water was used in the reaction.
d Aqueous sodium hydroxide was used as the solvent.

TABLE IX—Continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

A. Thiophenes^a—Continued

$$R_4 \underset{R_5}{\overset{R_3}{\underset{S}{\bigcirc}}} R_2 \quad (continued)$$

Substance Desulfurized	Product	Yield, %	References
$R_2 = CH_2(CH_2)_2CO_2H$, $R_5 = CH_2(OH)_3CH(C_2H_5)(CH_2)_3CH_3$	$C_6H_5(CH_2)_6CH(C_6H_5)CO_2H$	73[b]	164
$R_2 = OH{=}O(C_6H_5)OO_2H$, $R_5 = CH_2C_6H_5$	$C_6H_5(CH_2)_7CH(C_6H_5)CO_2H$	74	33
$R_2 = OH{=}O(C_6H_5)OO_2H$, $R_5 = CH_2CH_2C_6H_5$		—	33
$R_5 = O(CH_3)_2C_6H_5$		—	183
$R_2 = OH{=}O(C_6H_5)OO_2H$, $R_5 = CH_2(CH_2)_2C_6H_5$	$C_6H_5(CH_2)_8CH(C_6H_5)CO_2H$	—	33
$R_2 = CH_2(OH)_2CO_2H$, $R_5 = CH_2(OH)_7CO_2H$		—	168
$R_2 = CO_2H$, $R_5 = C_{16}H_{37}\text{-}n$		—	185
$R_2 = C_{16}H_{33}\text{-}n$, $R_5 = CHOH(CH_2)_2CO_2H$	$CH_3CH(OH)(CH_2)_{21}CH_3$	68	464
$R_2 = COCH_3$, $R_5 = C_{16}H_{37}\text{-}n$		83	185
$R_2 = C_{16}H_{33}\text{-}n$, $R_5 = CHOH(CH_2)_4CO_2H$		64	464
$R_2 = C_{12}H_{25}\text{-}n$, $R_5 = CHOH(CH_2)_6CO_2H$		75	464
$R_5 = O(C_6H_5)_2CH_3$		—	183
$R_2 = C_{18}H_{37}\text{-}n$, $R_5 = CHOH(CH_2)_8CO_2H$		75	464
$R_2 = CO_2H$, $R_4 = NO_2$, $R_5 = CH_3$	$CH_3CH_2CH(NH_2)CH_2CH_2CO_2H$	76	184f
$R_5 = CH_3$, $R_3 = CO_2H$		—[i]	171
$R_2 = CO_2H$, $R_4 = NO_2$, $R_5 = C_2H_5$	$CH_3(CH_2)_2CH(NH_2)CH_2CH_2CO_2H$	72	184f
$R_5 = CH_3$, $R_3 = CH(NH_2)CO_2H$		51[b]	175
$R_2 = CO_2H$, $R_4 = NO_2$, $R_5 = C_4H_9\text{-}i$	$(CH_3)_2CH(CH_2)_2CH(NH_2)CH_2CH_2CO_2H$	84	184f

$R_1 = CH_3$, or $R_1 = CHO$, $R_2 = C(OCH_3)_2$ (?)

$R_1 = R_4 = C_6H_5$, $R_2 = CO_2H$

$R_1 = R_4 = C(CH_3)_3$, $R_2 = CH_2CH_2CO_2H$

$R_1 = R_4 = C(CH_3)_3$, $R_2 = CHO$

$R_1 = R_4 = C(CH_3)_3$, $R_2 = COCH_3$

$R_1 = R_4 = C_6H_5$, $R_2 = CH(CH_3)CO_2H$

$R_1 = CH_3$, $R_2 = R_3 = CO_2H$

$R_1 = R_4 = CH_3$, $R_2 = CO(CH_2)_2CO_2H$, $R_3 = C_2H_5$

$R_1 = R_4 = C(CH_3)_3$, $R_2 = R_3 = CH_2OCH_3$

$R_1 = R_4 = CH_3$, $R_2 = CHO$

$R_1 = R_3 = CO_2H$, $R_2 = R_4 = C_6H_5$

$(CH_3CH_2CH(OH)CH_2CH(OH)CH_2CH_2CH_2CH_3$

(a)' 1,2,3,4-tetraphenylbutane

(b)' $C_6H_5CH_2CH_2C_6H_5$ and 1,2,3,4-tetraphenylbutane

	83, —	34
		168, 171
	53	172
		34
		31
		172
		169
		163
		182
	56	169
	78	98
	I'₀₀	98
	67	105
	—	465

HO₂C ⟨thiophene⟩ CO₂H

HO₂C ⟨thiophene⟩ CH₃

CO₂H ⟨thiophene⟩ CO₂H

HO₂C ⟨thiophene⟩ CH₃

Note: References 265 to 400 are on pp 625–629.

* Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

b Aqueous sodium carbonate was used as the solvent.

c Aqueous sodium hydroxide was used as the solvent.
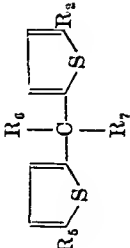
d Desulfurization did not occur.

e n-Butanol was employed as the solvent.

f Xylene was employed as the solvent.

TABLE IX—Continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIOAZOLES

A. Thiophenes[a]—Continued

Substance Desulfurized	Product	Yield, %	References
(thiophene structure with R_6, R_7, R_2, R_5 on ring $-C-$)			
$R_2 = HC$ (epoxide)	1-Decanol	33	184b
$R_2 = CHO$		35	173
$R_2 = CO_2H$		—	179
$R_2 = CH_2CH_2OH$		76	179
$R_2 = CH_2(CH_2)_2CO_2H$		66b	181
$R_2 = CH_2(CH_2)_3CO_2H$		73b	181
$R_2 = H_2C$ (structure)		59	173
$R_2 = CHO, R_5 = CH_3$	1-Undecanol	64	34
$R_2 = CO_2H, R_5 = CH_3$		69	184d
$R_2 = R_5 = CO_2H$		—b	107
$R_2 = CO_2H, R_5 = CH_2CH_2OH$		94b	180
$R_2 = R_5 = CH_2CH_2OH$		80	179
$R_2 = CO_2H, R_5 = CH_2(OH)_2CO_2H$		—	168
$R_2 = CH_2CH_2OH, R_5 = CH_2N(C_2H_5)_2$		45	178

	P%[a]	Ref.
$R_1 = R_2 = CH_2CH_2CO_2H$	69[a]	180
$R_1 = R_2 = CH(CH_3)CO_2H$	66	181
$R_1 = CH_2N(C_2H_5)_2$, $R_3 = CH_3$, $R_2 = C_2H_5$		177
$R_1 = HO\langle\cdots\rangle$, $R_2 = CH_3$, $R_3 = C_2H_5$	43	184b
$R_2 = CH_2CH_2OH$, $R_1 = CH_2N(C_2H_5)_2$, $R_3 = CH_3$,		178
$R_3 = R_1 = C_2H_5$		
$R_1 = R_3 = CO_2H$, $R_2 = CH_3$	63[b]	164
$R_2 = CO_2H$, $R_1 = C(CH_2)_4$ $\diagdown S \diagup$ CO_2H		109
$R_1 = R_2 = CH_3$	71	184d
		184e

Note: References 205 to 490 are on pp 525-529.

[a] Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not obtained.

[b] Aqueous sodium carbonate was used as the solvent.

[c] Aqueous sodium hydroxide was used as the solvent.

TABLE IX—Continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

A. Thiophenes[a]—Continued

Substance Desulfurized	Product	Yield, %	References
(CH₂)ₙCO ... CO(CH₂)ₙ [bithiophene structure]			
$n = 5$		90	184, 184e
$n = 8$		—, 64	184, 184e
$n = 9$		—, 68	184, 184e
CH₃CO—[terthiophene]—COCH₃		89	105
[benzothiophene structure with R_2, R_3, R_4, R_5, R_6, R_7]			
$R_2 \ldots R_7 = H$	$C_6H_5CH_2CH_3$	75	457
$R_3 = OH$		86	457
$R_4 = OH$		42	200
$R_4 = CO_2H$		93	466
$R_3 = CO_2H$		93	457
$R_3 = COCH_3$	$CH_3COOH(C_2H_5)CH_3$ and unidentified oil	—	14
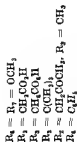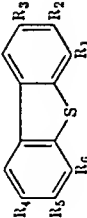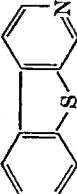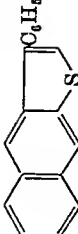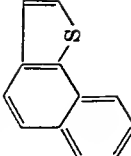
Reactant	Product	Yield (%)	Reference
$R_1 = R_2 = OCH_3$	Sweet-smelling oil[a]	—	409
$R_2 = CH_2CO_2H$		85	406
$R_2 = CH_2CO_2H$		98	406
$R_4 = C(CH_3)_3$		98	470
$R_4 = CH_2COCH_3, R_3 = CH_3$		94	467
$R_4 = C_2H_5$			466
$R_4 = p\text{-}CH_3OC_6H_4$	Biphenyl	—	255
$R_2 = C_6H_5, R_4 = CH_3$		—	255
$R_4 = C_6H_5, R_1 = CH_3$		—	255
$R_4 = C_6H_5, R_3 = CH_3$		—	255
$R_2 = C_6H_5, R_3 = OCH_3$		—	255
$R_2 = C(C_6H_5)_3CO_2H$		82	457
(structure)		—	471
(structure)		—	472

Note. References 205 to 480 are on pp. 525–529.

[a] Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

[b] Ethylene glycol was used as the solvent. Oxidation of the product gave veratric acid.

TABLE IX—Continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

A. Thiophenes—Continued

Substance Desulfurized	Product	Yield, %	References
(dibenzothiophene) $R_1 \ldots R_6 = H$	Biphenyl	98, 66, —,	14, 3, 457, 194
$R_2 = Br$		—	104
$R_1 = R_6 = OH_3$		31	104
$R_1 = R_3 = R_4 = R_6 = OH_3$		} —	103, 473
(pyridine-fused thiophene)		—	474
(C_6H_5 thiophene)		—	475
(phenanthro-thiophene)		50, —	476, 477

50	251
—	43
—	43
88	251
67	251

Note: References 265 to 490 are on pp. 525–529.

a Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

R = H
R = OCH₃

TABLE IX—*Continued*
RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
	A. Thiophenes—*Continued*		
	(?)	—	53
		—^{n}	102
	$CH_3CHOH(CH_2)_2C(OH_3)CH_2CH_3$	—	478
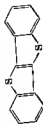
479, 478   —

13   66

    55

251   39

$(C_2H_5OH)_2$ C_2H_5 C_2H_4

H_3C— H_3C—

Note: References 265 to 490 are on pp. 525–529.

* Products arising from complete hydrogenation of the thiophene nucleus and replacement of sulfur by hydrogen are not shown.

* A special W-7 Raney nickel was employed.

TABLE IX—Continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References

B. Thiazoles

Product: $R_1CH_2CH_2CONHR_2$

		Yield, %	References
$R_1 = C_6H_5$		70	221
$R_1 = p\text{-}ClC_6H_4$		82	221
$R_1 = p\text{-}CH_3OC_6H_4$		80	221
$R_1 = p\text{-}(CH_3)_2NC_6H_4$		78	221
$R_1 = 3,4\text{-}CH_2O_2C_6H_3$		73	221
$R_1 =$ (tetrahydrofuran)		85	221
$R_1 = p\text{-}NH_2C_6H_4$		Fair	221
$R_1 = p\text{-}CH_3OC_6H_4$, $R_2 = C_2H_5$		80	221
$R_1 = p\text{-}(CH_3)_2NC_6H_4$, $R_2 = C_2H_5$		77	221

Substance Desulfurized:

$R_1 = p\text{-}NO_2C_6H_4$
$R_1 = p\text{-}CH_3OC_6H_4$, $R_2 = C_2H_5$
$R_1 = p\text{-}(CH_3)_2NC_6H_4$, $R_2 = C_2H_5$

$R_1 = $, $R_2 = C_4H_9$	54	221
$R_1 = p\text{-}NO_2C_6H_4$, $R_2 = C_4H_9$	78	221
$HO_2C(CH_2)_3CH(OH)CH_2CO_2H$	—	215
$CH_3CO\cdot NHC_2H_5$	—	42
$CH_3CH(NH_2)CO_2H$	60	490

TABLE IX—*Continued*

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
	B. Thiazoles—Continued		
$R_1 \ldots R_3 = H$	(*a*)	—	285
	(*b*) HOCH$_2$CH$_2$	—	285
	Vitamin B$_1$		
$R_1 = COCH_3$, $R_2 = R_3 = H$	Vitamin B$_1$ acetate	—	285
$R_1 \ldots R_3 = COCH_3$	Vitamin B$_1$	—	285
$R_3 = C_6H_5$	(*a*)^o C$_6$H$_5$CH(CH$_3$)NH$_2$	25	41
	(*b*)^p C$_6$H$_5$CH(NH$_2$)CH$_3$	20	41
	C$_6$H$_5$COCH$_3$	10	
	CH$_3$NH$_2$	—	

R₁ = NH₂, R₂ = OH	(a) CH₂CONHCHO	—	42
	(b) CH₂CONH₂	91	43
R₁ = NH₂, R₃ = C₂H₅	(c) C₂H₅COCH₃	45	43
	C₂H₅NH₂	13	
	C₂H₅CH₂CH₂CH₃	0	
	(d)ᵃ C₂H₅CH₂CH(NH₂)CH₃, CH₃NH₂, and NH₃	Fair	41
R₁ = I-C₄H₉, R₃ = C₆H₅	(e)ᵇ C₂H₅CH(NH₂)₂CH₃, and C₂H₅COCH₃	28	41
	C₂H₅CHO	19	41
	C₂H₅CH(NH₂)₂CH₃	—	41
R₁ = NH₂, R₄ = CH₂CH₂NHCOCH₃, R₄ = CO₂C₂H₅	I-C₄H₉CHO, C₂H₅COCH₃, i-C₄H₉CH₃, and	30	481
R₁ = OH, R₃ = NH₂, R₄ = CO₂C₂H₅	CH₃CH₂NHCOCH₃CH₂CONH₂	20	100
R₁ = NH₂, R₃ = C₂H₅, R₂ = CH₃	(e)ᶜ C₂H₅CH₂COCH₃, C₂H₅CH₂CH(NH₂)₂CH₃ and NH₃	—	41
R₁ = OH, R₃ = NH₂, R₄ = C₂H₅	(b)ᶜ C₂H₅CH₂COCH₃, and NH₃	—	
		33	196

Note: References 205 to 490 are on pp. 525–529.

ᵃ W-7 Raney nickel in methanol was used.
ᵇ W-2 Raney nickel in methanol was used.
ᶜ Employing either W-6 or W-7 Raney nickel and methanol solution.

TABLE IX—continued

RANEY NICKEL DESULFURIZATION OF THIOPHENES AND THIAZOLES

Substance Desulfurized	Product	Yield, %	References
	B. Thiazoles—Continued		
R = H	(a) $C_6H_5NHCH_3$	84–86, —	41, 50
	(b)^r $C_6H_5NHCH_3$,	7	41
	$C_6H_5NH_2$	20	
	(c)^s	0.2	41
R = CH$_3$	$C_6H_5NHCH_2CH_3$	—	41

Note: References 265 to 400 are on pp. 525–529.

^{r} Sodium hydroxide in methanol was used.

^{s} A special W-7 Raney nickel in xylene was employed.
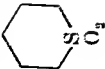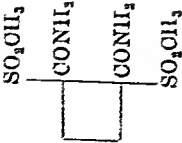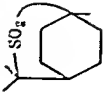
TABLE X

RANEY NICKEL DESULFURIZATION OF SULFOXIDES
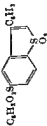
Sulfoxide	Product[*]	Yield, %	References
$[CH_3SO(CH_2)_2NH]_2CO$		—	200
$(C_6H_5)_2SO$		75	7, 198
$C_6H_5CH(OH)SO(CH_3)_2CH_3$	$C_6H_5COCH_3 + C_6H_5CH(OH)CH_3$	60	199
$C_6H_5C(CH_3)(CONH_2)SOC_6H_4$			17
(structure with SOC_6H_5, OH)	Indane	20	70
(structure with OH, SOC_6H_5)		—	70
(dibenzothiophene-type structure with O)	Unidentified oil	—	194
Sulfoxide of 3β-acetoxy-16-thiobenzylpregnen-20-one		75	101
Sulfoxide of 3-benzyl thio enol ether of Δ-androsten-3,17-dione		58	101

Note: References 205 to 400 are on pp. 525–529.

[*] Products resulting from replacement of sulfur by hydrogen are not shown.

TABLE XI
RANEY NICKEL DESULFURIZATION OF SULFONES

Sulfone	Product*	Yield, %	References
$(n\text{-}C_3H_7)_2SO_2$		†	58
$(n\text{-}C_4H_9)_2SO_2$		†	58
		†	78
	cis	—	484
	cis-p-Menthane	—	342
	cis- and trans-p-Menthane	—	342

	65, —	7, 60, 201
$(C_6H_5)_3SO$,		482
$C_6H_5CH_2SO_2C_6H_4CH_2CH_2CO_2H$	72	311
$C_6H_5CH_2SO_2C_6H_4COSH_2$	67	10
$C_6H_5C(CH_3)(CONH_2)SO_2C_6H_5$	78	482
$[C_6H_{10}S(SO_2)C_6H_4]_x$	63	482
	42	16
$(t\text{-}C_4H_9)_2CHSO_2C_2H_5$		202
$C_6H_5C(CH_3)(CO_2C_2H_5)SO_2C_2H_5$	Poor	483
$(C_2H_5O_2C)C_6H_4CH_2CH(CH_3)N(CH_3)_2$	Poor	483
$C_6H_5CH_2CH(CH_3)(SO_2)CH_2C_6H_4$	43	307
$(C_6H_5)_3CH_2CHC_6H_4$	40	307
cis-3 Methyl 3-benzoxosulfonylcyclohexyl β-naphthalate		
trans-3-Methyl-3-benzoxsulfonyl[cyclohexyl] β-naphthalate		
$(C_3H_7)_2CHCH_2$	61	307
$C_6H_5O_2S_2$,	—	475
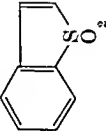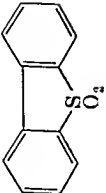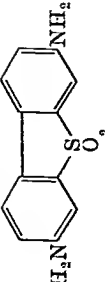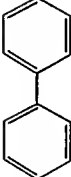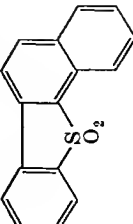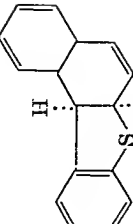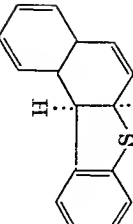
Note: References 265 to 490 are on pp. 525–529.

* Products representing only replacement of sulfur by hydrogen are not shown
† Desulfuration was not observed.
‡ Desulfuration was not observed when Raney nickel in ethanol was used.

TABLE XI—*Continued*

RANEY NICKEL DESULFURIZATION OF SULFONES

Sulfone	Product*	Yield, %	References
(benzothiophene sulfone)	Unidentified oil	—	203a
(dibenzothiophene sulfone)	Unidentified oil	—	194
(diaminodibenzothiophene sulfone)	C_2H_5NH—⟨biphenyl⟩—NHC_2H_5	70	345
Thionaphthen sulfone dimer	$C_6H_5CH_2CH_3$	—	203
(structure)		—	485
(structure with H···H)		—	485a

Note: References 205 to 490 are on pp. 525–529.

* Products representing only replacement of sulfur by hydrogen are not shown.

TABLE XII

Raney Nickel Desulfurization of Sulfonic Acids, Esters, and Amides
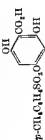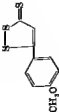
Substance Desulfurized	Product*	Yield, %	References
A. Sulfonic Acids			
$C_6H_5SO_2H$		10	205, 56
$o\text{-}HO_2C_6H_4SO_2H$		40	205
$m\text{-}HO_2C_6H_4SO_2H$		50	205
$R_2 = H, H$		40	205
$R_1 = OH$		30	205
$R_1 = OH, R_1 = SO_3H$		30	205
B. Sulfonate			
1,2-3,4,6-Tetraacetylglucose benzylsulfonate	Unabraided oil	—	206
1,2-3,4-Diisopropylidenegalactose benzylsulfonate	Diisopropylidenegalactose	95	206
1,2-5,6-Diisopropylideneglucose benzylsulfonate	Diisopropylideneglucose	100	206
2,3,4-Triacetyl-β-phenylglucoside-p-toluenesulfonate	Unidentified oil	—	206
1,2-Isopropylideneglucose 3,5-di-p-toluenesulfonate	1,2-Isopropylideneglucose	25	206
1,2-Isopropylideneglucose 6-p-toluenesulfonate	1,2-Isopropylideneglucose	39	206
1,2-5,6-Diisopropylideneglucose p-toluenesulfonate	1,2-5,6-Diisopropylideneglucose	94	206
		—	486
p-$CH_3C_6H_4SO_3H$			
5-Hydroxy-7-tosyloxyflavone	5-Hydroxyflavone	—	208

3-Methoxy-5-hydroxy-7-tosyloxyflavone → 5-Hydroxy-3-methoxyflavone — | — 208

5-Hydroxy-3,3',4'-trimethoxy-7-tosyloxyflavone → 5-Hydroxy-3,3',4'-trimethoxyflavone — | — 209

p-CH$_3$C$_6$H$_4$SO$_2$O ... CH$_3$CO$_2$ (steroid tosyloxy structure) → (steroid OH structure) CH$_3$CO$_2$ — | 207

C. Sulfonamides

C$_6$H$_5$CH$_2$SO$_2$NHC$_6$H$_5$ → C$_6$H$_5$NH$_2$ — 53 | 206

(benzisothiazolone structure, CO, NCH$_2$C$_6$H$_5$, SO$_2$) — 70 | 210

(benzisothiazolone structure, CO, N(CH$_2$)$_{11}$CH$_3$, SO$_2$) → (cyclohexyl)CONH(CH$_2$)$_{11}$CH$_3$ — 81 | 51

(thiadiazine structure $O_2^{\cdot}$S–NR$_2$, R$_1$, R$_3$) → (C$_6$H$_5$NH)$_2$CO

R$_1$ = R$_3$ = H — 79 | 42
R$_1$ = CH$_3$ — | 42
R$_2$ = R$_3$ = C$_6$H$_5$ — | 42

Note: References 205 to 490 are on pp. 525–520.

* Products representing only replacement of sulfur by hydrogen are not shown.

TABLE XIII

RANEY NICKEL DESULFURIZATION OF MISCELLANEOUS ORGANIC SULFUR COMPOUNDS

Substance Desulfurized	Product*	Yield, %	Reference
$(CH_3CO)_2S$		33	51
$(C_2H_5O)_2SO$		—	56
$n\text{-}C_4H_9NCS$		—	50
$C_2H_5(SCH_2)_4$ (tetramer)	$C_2H_4(CH_2)_2{=}C(CH_2)_2C_2H_4$	18	218
[structure with CH_3, N–S, benzene ring]	$o\text{-}CH_3C_6H_4NH_2$	61	43
$C_2H_5CH_2CH_2CH_2$		00	38
$HO_2C(CH_2)_2CH(C_2H_4)C_6SO_2H$		40	215
[structure with CH_3O-benzene ring]	$(p\text{-}CH_3OC_6H_4CH_2)_2h$	39–48	35
$(C_2H_5)_2$ [ring with $S{-}S$]		85	214

Note: References 205 to 490 are on pp. 525–529.

* Products representing only replacement of sulfur by hydrogen are not shown.

TABLE XIII—Continued
RANEY NICKEL DESULFURIZATION OF MISCELLANEOUS ORGANIC SULFUR COMPOUNDS
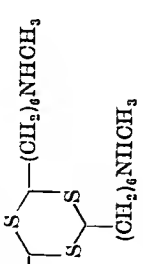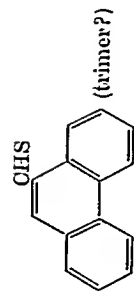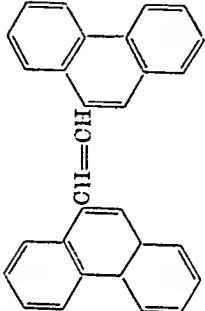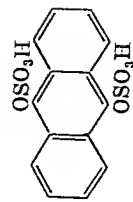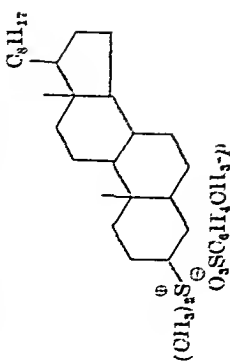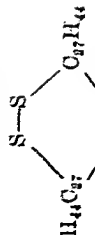
Substance Desulfurized	Product*	Yield, %	Reference
CH₃NH(CH₂)₆ [structure with S, S and (CH₂)₆NHCH₃, (CH₂)₆NHCH₃]	C₂H₅N(CH₃)(CH₂)₆CH₃†	—	487
Unknown intermediate	2,4,3'-Trimethylbiphenyl	—	488
[structure] CHS (trimer?)		20	210
C₆H₅SO₂H		—	50
[structure] OSO₃H, OSO₃H	Unidentified product‡	—	220
Leuco benz[a]anthracene-7,12-dione sulfuric ester	Benz[a]anthracene§	—	480
Leuco 4-chloro-3-methylbenz[a]anthracene-7,12-diono sulfuric ester	3-Methylbenz[a]anthracene§	—	480

Dibenzopyrene

1-Thioloxy-1-deoxy-2,4:3,5-dimethylene-DL-xylitol

1,2-Isopropylidene-5,6-duleoxy glucofuranose 5,6-trithiocarbonate

1:3,2,4-Diethylidene-5,6-dideoxy sorbitol 5,6-trithiocarbonate

1,2-3,4-Diisopropylidene-5,6-duleoxymannitol-5,6-trithiocarbonate

Dibenzopyrene (?)	—	220
	30	54
	45	301
	70	213
	—	217
	—	217
	—	217

Note: References 265 to 400 are on pp. 525–529.

* Products representing only replacement of sulfur by hydrogen are not shown.

† Ethanol was used as the solvent.

‡ The product gave anthracene after selenium dehydrogenation.

§ The product was dehydrogenated before isolation.

TABLE XIII—*Continued*

RANEY NICKEL DESULFURIZATION OF MISCELLANEOUS ORGANIC SULFUR COMPOUNDS

Substance Desulfurized	Product*	Yield, %	Reference
		—	490
($C_{27}H_{44}$=3-cholestery1-4-one)		—	354

Note: References 205 to 490 are on pp. 525–529.

* Products representing only replacement of sulfur by hydrogen are not shown.

[212] Badger, Kowanko, and Sasse, *J. Chem. Soc.*, **1960**, 1658.

[213] Weinstock and Lewis, *J. Am. Chem. Soc.*, **79**, 6243 (1957).

[214] Alderton and Fevold, *J. Am. Chem. Soc.*, **73**, 463 (1951).

[215] Teresa and Bellido, *Anales real soc. españ. fis. y quim.*, **52B**, 557 (1956) [*C.A.*, **51**, 6537 (1957)].

[216] Gregg, Iddles, and Stearns, *J. Org. Chem.*, **16**, 246 (1951).

[217] Stacy, Day, and Morath, *J. Am. Chem. Soc.*, **80**, 3475 (1958).

[218] Poppelsdorf and Holt, *J. Chem. Soc.*, **1954**, 1124.

[219] Vaterlaus and Furlenmeier, *Bull. soc. chim. France*, **1957**, 1481.

[220] Holley and Holley, *J. Am. Chem. Soc.*, **73**, 3172 (1951).

[221] Tatsuoka and Miyamoto, *J. Pharm. Soc. Japan*, **69**, 294 (1949) [*C.A.*, **44**, 2513 (1950)].

[222] Snyder, Cannon, Howe, and Nyman, *J. Am. Chem. Soc.*, **65**, 2211 (1943).

[223] Staněk, *Collection Czechoslov. Chem. Communs.*, **23**, 1154 (1958).

[224] Dodson, Peterson, and Seyler, *J. Am. Chem. Soc.*, **72**, 3281 (1950).

[225] Boarland and McOmie, *J. Chem. Soc.*, **1951**, 1218.

[226] McCarty, Haines, and Vanderwerf, *J. Am. Chem. Soc.*, **82**, 964 (1960).

[227] Grundmann, Ulrich, and Kreutzberger, *Chem. Ber.*, **86**, 181 (1953).

[228] Howard, Lythgoe, and Todd, *J. Chem. Soc.*, **1945**, 558.

[229] Holland, Lythgoe, and Todd, *J. Chem. Soc.*, **1948**, 965.

[230] Lythgoe, Smith, and Todd, *J. Chem. Soc.*, **1947**, 355.

[231] Baker, Schaub, and Joseph, *J. Org. Chem.*, **19**, 638 (1954).

[232] Anderson, Goodman, and Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959).

[233] Schmidt, Eichenberger, Wilhelm, and Druey, *Helv. Chim. Acta*, **42**, 349 (1959).

[234] Rose, *J. Chem. Soc.*, **1952**, 3448.

[235] Mozingo and Folkers, in *The Chemistry of Penicillin*, Princeton Univ. Press, p. 541, 1949.

[236] Ballard, Melstrom, and Smith, in *The Chemistry of Penicillin*, Princeton Univ. Press, p. 965, 1949.

[237] du Vigneaud and Carpenter, in *The Chemistry of Penicillin*, Princeton Univ. Press, p. 1004, 1949.

[238] Weisiger, Hausmann, and Craig, *J. Am. Chem. Soc.*, **77**, 3123 (1955).

[239] Peck and Folkers, in *The Chemistry of Penicillin*, Princeton Univ. Press, p. 159, 1949.

[240] Hodgson, Bick, and Cram, *J. Am. Chem. Soc.*, **76**, 1137 (1954).

[240a] Hočák and Černý, *Chem. Listy.*, **46**, 421 (1952) [*C.A.*, **47**, 3853 (1953)].

[241] Birch, Dean, and Whitehead, *J. Org. Chem.*, **19**, 1449 (1954).

[242] Weitkamp, *J. Am. Chem. Soc.*, **81**, 3434 (1959).

[243] Kao, Tilak, and Venkataraman, *Proc. Indian Acad. Sci.*, **32A**, 162 (1950).

[244] Blackhall and Thomson, *J. Chem. Soc.*, **1953**, 1138.

[245] Shah, Tilak, and Venkataraman, *Proc. Indian Acad. Sci.*, **28A**, 142 (1948) [*C.A.*, **44**, 3958 (1950)].

[246] Michels and Amstutz, *J. Am. Chem. Soc.*, **72**, 888 (1950).

[247] Machly and Reichstein, *Helv. Chim. Acta*, **30**, 499 (1947).

[248] Grob and Prins, *Helv. Chim. Acta*, **28**, 840 (1945); Jeanloz, Prins, and Reichstein, *ibid.*, **29**, 371 (1946).

[249] Newth, Richards, and Wiggins, *J. Chem. Soc.*, **1950**, 2356.

[250] Davoll, Lythgoe, and Trippett, *J. Chem. Soc.*, **1951**, 2230.

[251] Hough and Tahn, *J. Chem. Soc.*, **1956**, 2042.

[252] Sarett, *J. Am. Chem. Soc.*, **71**, 1175 (1949).

[253] Jeanloz, *J. Am. Chem. Soc.*, **72**, 2281 (1950).

[254] Bourdon, *Bull. soc. chim. France*, **1958**, 722.

[255] Stewart and Cordts, *J. Am. Chem. Soc.*, **74**, 5880 (1952).

[256] Brockman, Stokstad, Patterson, Pierce, Macchi, and Day, *J. Am. Chem. Soc.*, **74**, 1868 (1952).

[257] Reed, Gunsalus, Schnakenberg, Soper, Boaz, Kern, and Parks, *J. Am. Chem. Soc.*, **75**, 1267 (1953).

[258] Celmer and Solomons, *J. Am. Chem. Soc.*, **77**, 2861 (1955).

[410] Heusser, Eichenberger, Kurath, Dällenbach, nnd Jeger, *Helv. Chim. Acta*, 34, 2106 (1951).

[411] Fieser, Babcock, Herz, Huang, and Schneider, *J. Am. Chem. Soc.*, 73, 4053 (1951).

[412] DeVries and Backer, *Rec. trav. chim.*, 69, 759 (1950).

[413] DeVries and Backer, *Rec. trav. chim.*, 69, 1252 (1950).

[414] Sato and Ikekawa, *J. Org. Chem.*, 24, 1367 (1959).

[415] Louw, Strating, and Backer, *Rec. trav. chim.*, 73, 655 (1954).

[416] Ralls, *J. Am. Chem. Soc.*, 75, 2123 (1953).

[417] Sheehan and Erman, *J. Am. Chem. Soc.*, 79, 6050 (1957).

[418] Burgstahler and Nordin, *J. Am. Chem. Soc.*, 81, 3151 (1959).

[419] Eastham, Miles, and Krauth, *J. Am. Chem. Soc.*, 81, 3114 (1959).

[419a] Scheer, Thompson, and Mosettig, *J. Am. Chem. Soc.*, 79, 3218 (1957).

[419b] Fieser and Huang, *J. Am. Chem. Soc.*, 75, 5336 (1953).

[420] Woodward, Patchett, Barton, Ives, and Kelly, *J. Chem. Soc.*, 1957, 1131.

[421] Golab, Trabert, Jeger, and Reichstein, *Helv. Chim. Acta*, 42, 2418 (1959).

[422] Djerassi, Fishman, and Moore, *Chem. & Ind. (London)*, 1320 (1954).

[423] Pettit and Bowyer, *J. Org. Chem.*, 25, 84 (1960).

[424] Djerassi, Batres, Velasco, and Rosenkranz, *J. Am. Chem. Soc.*, 74, 1712 (1952).

[425] Klass, Fieser, and Fieser, *J. Am. Chem. Soc.*, 77, 3829 (1955).

[426] Djerassi, Ringold, und Rosenkranz, *J. Am. Chem. Soc.*, 73, 5513 (1951).

[427] Schrötor, Tamm, and Reichstein, *Helv. Chim. Acta*, 41, 729 (1958).

[428] Voser, Montavon, Gunthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 33, 1893 (1950).

[429] Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 35, 503 (1952).

[430] Brovet, *Arkiv Kemi*, 20, 70 (1948) [*C.A.*, 44, 6829 (1950)].

[431] Burger, Rector, and Schmalz, *J. Am. Chem. Soc.*, 74, 3175 (1952).

[432] Boekelheide and Lodge, *J. Am. Chem. Soc.*, 73, 3681 (1951).

[433] Turner, *J. Am. Chem. Soc.*, 70, 3961 (1948).

[434] Staněk, *Chem. Listy*, 45, 459 (1951) [*C.A.*, 46, 7567 (1952)].

[435] Edward and Martlew, *Chem. & Ind. (London)*, 1954, 193.

[436] Staněk and Šídlo, *Chem. Listy*, 47, 471, (1953) [*C.A.*, 48, 3370 (1954)].

[437] Gompper, *Chem. Ber.*, 89, 1762 (1956).

[438] Staněk and Šídlo, *Českoslov. farm.*, 2, 117 (1953) [*C.A.*, 49, 6123 (1955)].

[439] Staněk and Šídlo, *Chem. Listy*, 47, 470 (1953) [*C.A.*, 48, 3354 (1954)].

[440] Taylor, *J. Am. Chem. Soc.*, 74, 6295 (1952).

[441] Bestmann and Schulz, *Chem. Ber.*, 92, 539 (1959).

[442] Okumura, Masumura, and Horie, *Yûki Gôsei Kagaku Kyokai Shi*, 17, 415 (1959) [*C.A.*, 53, 17057 (1959)].

[443] Brown and Newbold, *J. Chem. Soc.*, 1952, 4397.

[444] McIntosh, Meinzer, and Levin, *J. Am. Chem. Soc.*, 70, 2955 (1948).

[445] Jensen, *Paper and Timber (Finland)*, 32, 293 (1959) [*C.A.*, 46, 8996 (1952)].

[446] Djerassi and Pettit, *J. Org. Chem.*, 22, 393 (1957).

[447] Prijs, Lutz, and Erlenmoyer, *Helv. Chim. Acta*, 31, 571 (1947).

[448] Heer and Miescher, *Helv. Chim. Acta*, 30, 777 (1947).

[449] Okumura, Masumura, and Horio, *Yûki Gôsei Kagaku Kyokai Shi*, 17, 419 (1959) [*C.A.*, 53, 17058 (1959)].

[450] Okumura, Masumura, Horie, and Kori, *Yûki Gôsei Kagaku Kyokai Shi*, 17, 461 (1959) [*C.A.*, 53, 21794 (1959)].

[451] Prelog, Norymberski, and Jeger, *Helv. Chim. Acta*, 29, 369 (1946).

[452] Dreiding, Jeger, und Ruzicka, *Helv. Chim. Acta*, 33, 1325 (1959).

[453] Jeger, Nisoli, and Ruzicka, *Helv. Chim. Acta*, 29, 1183 (1946).

[453a] van Tamelen, Aldrich, and Hester, *J. Am. Chem. Soc.*, 81, 6214 (1959).

[454] Bonner and Kahn, *J. Am. Chem. Soc.*, 73, 2241 (1951).

[455] Hardegger and Montavon, *Helv. Chim. Acta*, 29, 1199 (1946).

[456] King and Campbell, *J. Am. Chem. Soc.*, 71, 3556 (1949).

[457] Blicke and Sheets, *J. Am. Chem. Soc.*, 71, 4919 (1949).

[458] Gronowitz, *Arkiv Kemi*, 13, 87 (1958) [*C.A.*, 53, 17991 (1959)].

[434] Grey, McGhie, Pradhan, and Ross, *Chem. & Ind.* (London), 1954, 578.

[435] Gronowitz, *Arkiv Kemi*, 12, 239 (1958) [*C A.*, 52, 20115 (1958)].

[436] Spaeth and Germann, *J. Am. Chem. Soc.*, 77, 4066 (1955).

[437] Fabrichnyi, Shalavina, and Gol'dfarb, *Zhur. Obshchee Khim.*, 28, 2520 (1958) [*C A.*, 53, 3052 (1959)].

[438] Sy, *Bull. soc. chim. France*, 1955, 1175.

[439] Miller, Haymaker, and Gilman, *J Org Chem.*, 24, 922 (1959).

[440] Lesont, Huu-Hoi, and Xuong, *J Chem Soc.*, 1959, 3234.

[441] Blicke and Sheets, *J Am Chem Soc*, 70, 3768 (1948).

[442] Gaertner, *J. Am. Chem. Soc.*, 74, 2991 (1952).

[443] Gaertner, *J. Am. Chem. Soc.*, 74, 4950 (1952).

[444] Banfield, Davies, Ennis, Middleton, and Porter, *J Chem Soc*, 1956, 2603.

[445] Corson, Tiefenthal, Atwood, Heintzelman, and Reilly, *J. Org Chem.*, 21, 584 (1956).

[446] Birch, Cullum, Dean, and Redford, *Tetrahedron*, 7, 311 (1959).

[447] Dann, Kokorudz and Gropper, *Chem Ber*, 87, 140 (1954).

[448] Carruthers and Douglas, *J. Chem Soc*, 1959, 2813.

[449] Kotake and Sakan, *J. Inst. Polytech Osaka City Univ., Ser C*, 2, No. 1, 25 (1951).

[450] Dann and Kokorudz, *Chem. Ber.*, 91, 172 (1958).

[451] Kruber and Raenthal, *Chem Ber*, 86, 366 (1953).

[452] Carruthers, *J. Chem Soc.*, 1953, 4786.

[453] Challenger and Holmes, *J Chem Soc.*, 1953, 1837.

[454] Challenger, Fishwick, and Holmes, *Chem. & Ind*, 1952, 519.

[455] Behringer and Zillikens, *Ann.*, 574, 140 (1951).

[456] Marrian, *J Chem. Soc.*, 1949, 1797.

[457] Cronyn, *J Am Chem Soc*, 74, 1225 (1952).

[458] Ternaa and Bellido, *Anales real soc. españ. fís. y quim.* (Madrid), 52B, 383 (1956) [*C A.*, 51, 6537 (1957)].

[459] Gundermann and Huchting, *Chem. Ber.*, 92, 415 (1959).

[460] Davies, James, Middleton, and Porter, *J. Chem Soc.*, 1955, 1565.

[461] Bordwell, McKellin, and Babcock, *J. Am. Chem. Soc.*, 73, 5566 (1951).

[462] Ramanathan and Venkataraman, *Current Sci.* (India), 21, 293 (1952) [*C A.*, 47, 9961 (1953)].

[463] Leonard and Musker, *J. Am. Chem. Soc.*, 81, 5631 (1959).

[464] Ruhr, Hansen, Knutson, and Koller, *J. Am. Chem. Soc.*, 80, 5517 (1958).

[465] Desai and Venkataraman, *Tetrahedron*, 3, 395 (1958).

[466] Blau and Stuckwisch, *J. Org. Chem.*, 25, 1611 (1960).

AUTHOR INDEX, VOLUMES 1-12

CHAPTER INDEX, VOLUMES 1–12

Since the tables of contents of the individual chapters provide a quite complete index, only those items not readily found on the contents pages are indexed here

Numbers in boldface type refer to experimental procedures